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Drug Development® & Delivery

May 2021 Vol 21 No 4 www.drug-dev.com

How COVID-19 Changed the PFS & Parenteral Manufacturing Market

The Science & Business of Pharmaceutical and Biological Drug Development

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DAI HAYWARD

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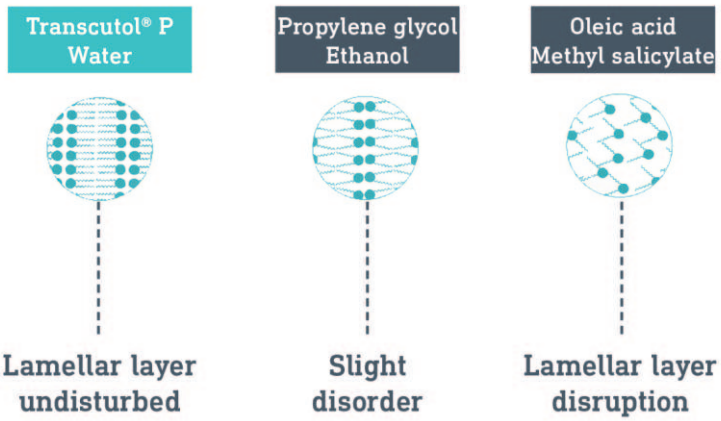

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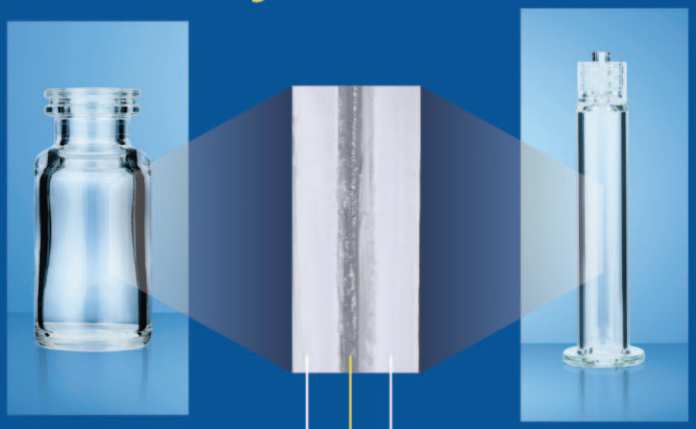

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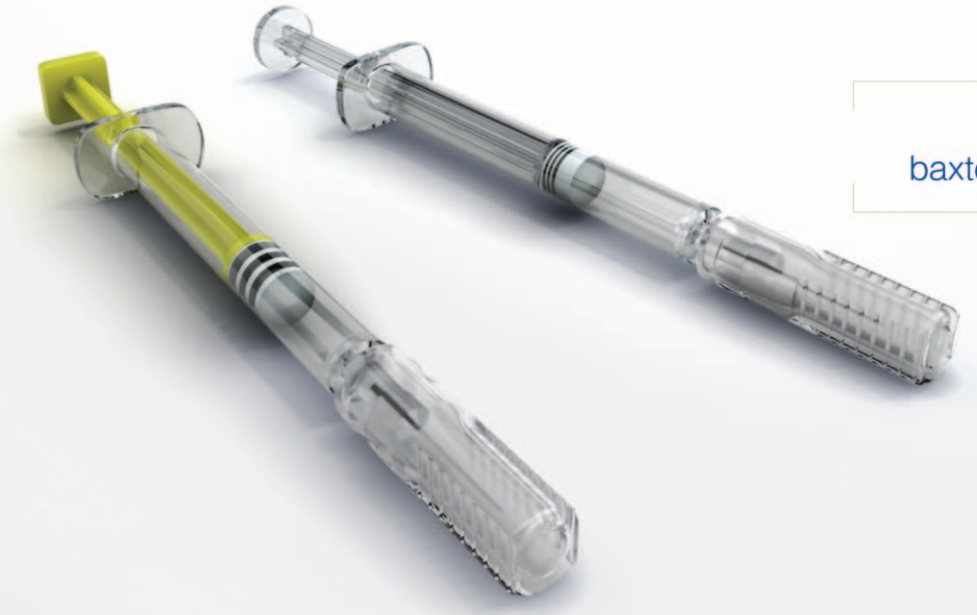

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PFS & Parenteral Manufacturing

"Research on the global PFS drug molecules market shows that among drug classes, vaccines and insulin are expected to be top competitors during the forecast period. However, vaccines lead the market with a projected revenue of over $23 billion by the end of 2027, while insulin will have a higher growth rate. Experts agree this can be attributed to the COVID-19 pandemic."

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THE DIFFERENCE OF ONE DRUG DELIVERED

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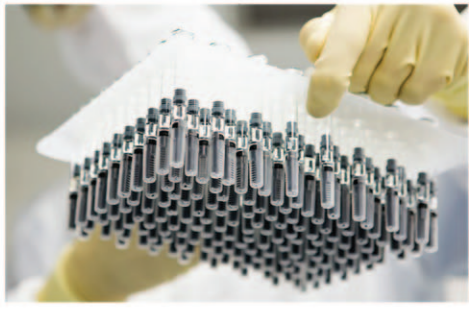

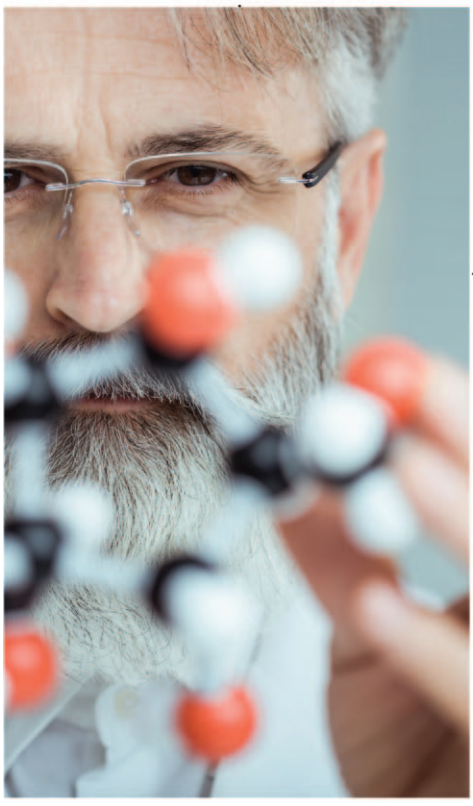

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Agenus Submits Balstilimab Biologics License Application to the US FDA for Patients With Recurrent or Metastatic Cervical Cancer

Agenus Inc. recently announced the submission of a Biologics License Application (BLA) to the US FDA for the accelerated approval of balstilimab, Agenus' anti-PD-1 antibody, for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy, and includes data from its pivotal Phase 2 single-arm clinical trial, presented at the European Society for Medical Oncology (ESMO) Virtual Congress 2020. These clinical data, along with preclinical data, suggest that balstilimab demonstrates differentiated features from other anti-PD-1 antibodies.

"Women with recurrent or metastatic cervical cancer have a very poor prognosis and limited treatment options. Data suggest balstilimab may bring benefit to patients beyond what is available in this disease setting today," said Jennifer Buell, PhD, President and Chief Operating Officer at Agenus. "This submission also marks a significant step in our transition to a commercial company and the advancement of our oncology combination strategy."

The balstilimab BLA submission is based on an update to data presented at the ESMO Virtual Congress 2020 and published in an Oncogene editorial, which demonstrate that balstilimab shows potential differentiation from other anti-PD-1 antibodies. This updated dataset includes maturation of late patient responses, with the overall data showing response rates of 20% in PD-L1 positive tumors, 15% in all tumors (PD-L1 positive and negative), and a median duration of response of 15.4 months.

"We expect that the potential approval of balstilimab will enable us to better pursue our oncology combination strategy for our own extensive pipeline of agents as well as for existing and future partner products," said Steven O'Day, MD, Chief Medical Officer at Agenus. "In particular, we hope to use this potential approval to allow us to rapidly proceed with our anti-CTLA-4 combination strategy, which we believe can add significantly to the benefit provided by our anti-PD-1 agent. There are currently limited treatment options available for recurrent or metastatic cervical cancer patients, and our vision is to bring effective treatments to these patients."

In April 2020, the FDA granted Fast Track designation for balstilimab in recurrent or metastatic cervical cancer based on its potential to provide benefit to patients with a serious condition and unmet medical need. A global, randomized, Phase 3 confirmatory clinical trial designed to support global registration is planned.

Balstilimab is a novel, fully human monoclonal immunoglobulin G4 (IgG4) designed to block PD-1 (programmed cell death protein 1) from interacting with its ligands PD-L1 and PD-L2. PD-1 is a negative regulator of immune activation that is considered a foundational target within the immuno-oncology market. Balstilimab is currently in clinical trials as monotherapy and in combination with Agenus' anti-CTLA-4, zalifrelimab, in an ongoing Phase 2 study for recurrent/metastatic cervical cancer.

ERS Genomics & NUVISAN ICB Sign CRISPR/Cas9 License Agreement

ERS Genomics Limited and NUVISAN Innovation Campus Berlin (ICB) GmbH recently announced a non-exclusive license agreement granting NUVISAN ICB access to ERS Genomics' CRISPR/Cas9 patent portfolio.

NUVISAN ICB originated from a spin-out of the major pharma R&D functions of BAYER, which were acquired by NUVISAN in 2020. With its fully functional capabilities and capacities to support the entire drug discovery value chain, NUVISAN ICB offers integrated programs from target discovery to the clinic, including lead discovery, medicinal chemistry, pharmacology, drug metabolism, and investigational toxicology. NUVISAN ICB's growing list of new clients comprises top pharmaceutical and biotechnology companies, as well as start-ups and venture capital groups.

ERS Genomics holds an exclusive worldwide license from co-founder and recent Nobel prize winner Dr. Emmanuelle Charpentier to the foundational intellectual property covering CRISPR/Cas9 for use as a research platform.

Eric Rhodes, CEO of ERS Genomics, said "We are pleased to provide NUVISAN ICB access to this Nobel Prize winning technology, further expanding the reach of the important gene editing tool and enhancing NUVISAN's portfolio of service offering to organizations in the field of drug development."

Hans Lindner, Managing Director of NUVISAN ICB, added "CRISPR/Cas9 is revolutionizing drug development, and we are very pleased to now be able to add this capability to our service portfolio. The inclusion of CRISPR gene editing enables us to continue to meet our clients' needs, to help us advance their drug discovery and early development programs from the target to the patient."

Financial details of the agreement are not disclosed. ERS Genomics is a biotechnology company based in Dublin, Ireland. The company was formed to provide broad access to the foundational CRISPR/Cas9 intellectual property held by Dr. Emmanuelle Charpentier. Non-exclusive licenses are available for research and sale of products and services across multiple fields including: research tools, kits, reagents; discovery of novel targets for therapeutic intervention; cell lines for discovery and screening of novel drug candidates; GMP production of healthcare products; companion animal and livestock health; production of industrial materials such as enzymes, biofuels and chemicals; and synthetic biology. For more information, visit www.ersgenomics.com.

The NUVISAN group is a Contract Research Organization (CRO) and Contract Manufacturing Organization (CDMO) with its headquarters in Neu-Ulm and six sites in Germany and France (Neu-Ulm, Berlin, Grafing, Gauting, Waltrop and Sophia-Antipolis) in addition to monitoring activities with offices in Argentina, Peru, Brazil as well as in the US. NUVISAN offers integrated and coupled services and solutions along the drug development value chain from target identification to the patient, with all supporting services (DMPK, GMP synthesis, formulation development and analysis, bioanalysis, Phase 1 CPU, clinical trial supplies and monitoring). Having a proven track record to include over 40 years of continuous service is a testimony to the operational excellence and the experience of our 1,000 highly qualified employees.

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CureVac Swiss AG Initiates Rolling Submission Process for mRNA-Based COVID-19 Vaccine Candidate

The CureVac Swiss AG, the Swiss subsidiary of CureVac N.V. recently announced initiation of a rolling submission for CVnCoV, the company's mRNA-based COVID-19 vaccine candidate, for the use in Switzerland. The application for authorization was submitted to Swissmedic, the country's authority responsible for the authorization and supervision of therapeutic products including vaccines.

CureVac has already provided the first data package on CVnCoV, its COVID-19 vaccine candidate. Swissmedic will review these data regarding the standards of quality, safety, and efficacy in consideration of the potential authorization for use of the CureVac vaccine candidate in Switzerland. With this process the time to authorization can be reduced.

"Switzerland is an important market for CureVac not only with regards to CVnCoV," said Antony Blanc, Chief Business Officer (CBO) & Chief Commercial Officer (CCO). "Along with Germany and Austria, Switzerland represents one of the three countries for which CureVac holds exclusive commercialization rights for program products in the context of CureVac's broad GSK partnership in vaccines for infectious diseases as well as second-generation vaccines for COVID-19. After having established a legal entity in Basel in March 2021, we now took the next key step in preparing the timely access to Switzerland following our ongoing efforts for the European Union territory."

In early February, the Swiss federal government and CureVac have signed a contract for the supply of five million vaccine doses. The contract is based on the delivery agreement between the European Commission and the company.

CureVac's COVID-19 vaccine candidate is currently in late-stage clinical testing. The pivotal Phase 2b/3 study (HERALD), initiated on December 14, 2020, has successfully completed recruitment, with currently about 40,000 participants in Latin America and in Europe. In February 2021, the company started a rolling submission with the European Medicines Agency (EMA) for CVnCoV and, subject to the clinical trial results, expects the potential authorization for use in the EU in the second quarter of 2021.

CureVac began development of its mRNA-based COVID-19 vaccine candidates in January 2020. The vaccine candidate chosen first for clinical development, CVnCoV, is an optimized, non-chemically modified mRNA, encoding the prefusion stabilized full-length spike protein of the SARS-CoV-2 virus, and formulated within Lipid Nanoparticles (LNPs). Phase 1 and 2a clinical trials of CVnCoV began in June and September 2020, respectively. Phase 1 interim data reported in November 2020 showed that CVnCoV was generally well tolerated across all tested doses and induced strong antibody responses in addition to first indication of T cell activation. The quality of immune response was comparable to recovered COVID-19 patients, closely mimicking the immune response after natural COVID-19 infection. In December 2020, CureVac initiated a pivotal Phase 2b/3, the HERALD study, with a 12µg dose of CVnCoV. In February 2021, CureVac initiated a rolling submission with the European Medicines Agency (EMA) for CVnCoV.

SOTIO Demonstrates Strong Potential of SOT102 (ADC Targeting Claudin 18.2) for Treatment of Solid Tumors in Preclinical Studies

SOTIO recently announced new preclinical data of its antibody-drug conjugate (ADC), SOT102 (formerly SO-N102), for the treatment of solid tumors in a virtual poster presentation at the 2021 American Association of Cancer Research (AACR) Annual Meeting. The data, which demonstrate that SOT102 has strong potential to eliminate CLDN18.2-expressing tumor cells in a target-specific manner, provide proof of concept for SOT102 as well as SOTIO's proprietary ADC platform.

Data highlights from the poster entitled, SOT102, a novel CLDN18.2-targeting antibody-drug conjugate with strong therapeutic potential in solid tumors expressing low target levels include:

- SOT102 showed high specificity and binding affinity for CLDN18.2, as well as efficient tumor cell killing *in vivo*
- Complete responses were observed in all 10 patient-derived mouse xenograft models, including those for gastric, pancreatic, liver, colon and lung adenocarcinomas, independent of CLDN18.2 expression levels
- SOT102 demonstrated favorable tolerability and pharmacokinetic properties, with the latter substantiated by observed half-lives in the range of eight days and 13 days in cynomolgus monkey and rat, respectively
- Stability of SOT102 without significant loss of payload was demonstrated *in vitro* and *in vivo*.

"Antibody-drug conjugate therapies have exhibited great promise for the future of cancer treatments, however, successes have been limited by small therapeutic windows, pharmacokinetic limitations and severe safety concerns," said Radek Špíšek, MD, PhD, Chief Executive Officer of SOTIO. "The results from our preclinical proof-of-concept study of SOT102 not only demonstrate excellent signs of safety, tolerability and efficacy in vivo, but also molecular stability and a greatly expanded therapeutic window. These findings provide SOTIO strong rationale for proceeding with in-human studies, which we look forward to initiating in early 2022."

SOT102 is a CLDN18.2 targeting antibody-drug conjugate based on a proprietary, highly specific monoclonal antibody conjugated to a potent cytotoxic drug molecule and is being developed in collaboration with NBE-Therapeutics. IND-enabling studies of SOT102 are currently ongoing with an IND filing planned for the fourth quarter of 2021, followed by a first-in-human clinical study in patients with gastric and pancreatic cancer planned for the first half of 2022.

SOTIO is shaping the future of cancer immunotherapies by translating compelling science into patient benefit. SOTIO's robust clinical pipeline includes a differentiated superagonist of the attractive immuno-oncology target IL-15, a platform to streamline personalized active immune cell therapies, CAR T platform and a new generation of potent and stable antibody-drug conjugates (ADCs). SOTIO is a member of the PPF Group. For more information, visit www.sotio.com.

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Cidara Therapeutics Announces Agreement With Janssen to Develop & Commercialize AVCs for the Prevention & Treatment of Influenza

Cidara Therapeutics, Inc. recently announced it has entered into an exclusive worldwide license and collaboration agreement with Janssen Pharmaceuticals, Inc. to develop and commercialize Cidara's Cloudbreak antiviral conjugates (AVCs) for the prevention and treatment of seasonal and pandemic influenza. This agreement was facilitated by Johnson & Johnson Innovation.

Under the collaboration, Cidara will be responsible for the development and manufacturing of the first influenza AVC, CD388, into the clinic and through Phase 2 clinical development, and Janssen will be responsible for late-stage development, manufacturing, registration, and global commercialization. Cidara will receive an upfront payment of $27 million, and Janssen will fund all future research, development, manufacturing, and commercialization for CD388. In addition to the upfront payment, Cidara is eligible to receive up to an aggregate of $753 million in budgeted R&D funding and in development, regulatory and commercial milestones, plus tiered royalties on worldwide sales in the mid to high single digits. Cidara has the option to co-detail CD388 in the US.

"In the US alone, there are an estimated 100 million individuals who are at high risk for complications due to seasonal influenza, and each year, there are up to 650,000 influenza deaths worldwide. This collaboration represents a significant advancement toward fulfilling our vision of providing universal, seasonal protection against all seasonal and pandemic strains of influenza," said Jeffrey Stein, PhD, President and Chief Executive Officer of Cidara. "We believe Janssen, with its expertise in the development and commercialization of vaccines and therapies for viral respiratory diseases, is the ideal partner to rapidly advance CD388. Importantly, this agreement validates our Cloudbreak antiviral platform as we continue to advance our AVC programs in RSV, HIV and SARS-CoV-2."

CD388 is a long-acting antiviral immunotherapy designed to deliver universal protection for an entire influenza season. By targeting a highly conserved region on the influenza virus, CD388 has the potential to protect individuals from all influenza strains, including seasonal and pandemic influenza A, influenza B and major clinically characterized drug resistant influenza strains. CD388 retains its potent antiviral activity even in immunocompromised animal models of influenza infection and thus is expected to be clinically effective across all patient populations, regardless of immune status and circulating strains. Cidara expects to file an Investigational New Drug Application for CD388 with the U.S. Food and Drug Administration by the end of 2021.

Cidara is developing a new generation of immunotherapeutic antivirals from its Cloudbreak antiviral platform that couple potent antivirals to a human antibody fragment. These long-acting, antiviral conjugates (AVCs) directly inhibit viral proliferation while simultaneously engaging the immune system. AVCs being studied for the prevention and treatment of seasonal and pandemic influenza have the potential to deliver universal protection for an entire flu season. Cidara is also advancing preclinical and discovery AVC programs to target other life-threatening viruses, such as RSV, HIV and SARS-CoV-2 strains causing COVID-19.

Artelo Biosciences Doses First Patient in CAReS Study for the Treatment of Cancer-Related Anorexia & Weight Loss

Artelo Biosciences, Inc. recently announced the first patient has been dosed in the company's Phase 1/2 Cancer Appetite Recovery Study (CAReS) of ART27.13 in Edinburgh, Scotland, UK. ART27.13 is a peripherally selective G-Protein Coupled Receptor (GPCR) full agonist that is being developed as a much-needed therapy for cancer patients suffering from anorexia and weight loss, which affects over 60% of later-stage cancer patients, often impacts quality of life, and can hasten death.

"Commencing enrollment and dosing the first patient in our CAReS study marks another important milestone in advancing ART27.13, which we are developing for patients suffering from the devastating effects of cancer associated anorexia – a multi-billion-dollar addressable market with no pharmacologic standard of care," stated Andrew Yates, PhD, Senior Vice President and Chief Scientific Officer of Artelo. "Notably, we anticipate that we will be able to collect initial safety data from Phase 1 of CAReS before the end of this year, which will determine the most effective and safest dose of ART27.13 to utilize in Phase 2 of the study. ART27.13 has previously demonstrated weight gain in subjects with lower back pain and we look forward to conducting the study in anorexic cancer patients who have suffered significant weight loss."

ART27.13 is a highly potent, peripherally restricted synthetic, dual GPCR agonist believed to target the cannabinoid receptors CB1/CB2, which has the potential to increase appetite and food intake. Originally developed by AstraZeneca plc, ART27.13 has been in five Phase 1 clinical studies including over 200 subjects where it demonstrated a statistically significant and dose-dependent increase in body weight in healthy subjects. Importantly, the changes in body weight were not associated with fluid retention and the distribution of the drug enables systemic metabolic effects while minimizing central nervous system mediated toxicity. Artelo is advancing ART27.13 as a supportive care therapy for cancer patients suffering from anorexia and weight loss where the current annual global market is estimated to be valued in excess of $2 billion.

The Cancer Appetite Recovery Study (CAReS) is a Phase 1/2 randomized, placebo-controlled trial of the Company's lead clinical program, ART27.13, in patients with cancer anorexia and weight loss. Anorexia, or the lack or loss of appetite in cancer patients, may result from the cancer and/or its treatment with radiation or chemotherapy. It is common for patients with cancer to lose weight. Anorexia and the resulting weight loss can affect a patient's health, often weakening their immune system and causing discomfort and dehydration. A weight loss of more than 5% can predicted a poor outcome for cancer patients and a lower response to chemotherapy. The Phase 1 portion of the CAReS study is designed to determine the most effective and safest dose of ART27.13 that will be used in the Phase 2 stage. The Phase 2 portion of the CAReS study is designed to determine point estimates of activity of ART27.13 in terms of lean body mass, weight gain, and improvement of anorexia.

Catalent Adds Cryogenic Capabilities at Philadelphia Clinical Supply Services Facility to Meet Growing Demand for Cell & Gene Therapy Development

Catalent recently announced it has made an investment to expand capabilities at its clinical supply services facility in Philadelphia to support sponsors developing cell and gene therapies.

The investment has enabled part of the facility to be dedicated to the safe handling of cell and gene therapy samples, including the installation of cryogenic storage, allowing biological materials such as cell therapies to be preserved in liquid nitrogen vapor at temperatures of around minus 180 degrees Celsius. The facility also has the ability to package, label, and distribute cryogenic materials, ensuring the integrity of the therapies being prepared for clinical trials, and has been designed so that capacity can be rapidly expanded further to meet growing clinical supply needs, as well as future commercial demand.

"Establishing robust clinical supply chain services for cell and gene therapies is complex and challenging, and Catalent has undertaken an in-depth strategic review to evaluate how it can establish a safe, efficient, and flexible approach to support this fast-growing area of the industry," said Ricci Whitlow, President, Catalent Clinical Supply Services. "The solution we have implemented at Philadelphia not only meets current needs, but also provides a template for us to easily replicate at other facilities in our global network, allowing incremental capacity expansion within the new infrastructure as demand grows."

The 200,000-sq-ft Philadelphia facility is the largest site in Catalent's global clinical supply network, and the company's North American Center of Excellence for clinical supply packaging. It includes an on-site pharmacy to support FlexDirect direct-to-patient service for clinical trials, as well as offering customers access to Catalent's FastChain demand-led supply services, primary and secondary packaging capabilities, a range of temperature options for storage and distribution, and clinical returns and destruction services.

With sites in the US, UK, Germany, Singapore, Japan, and China, and an extended network of over 50 depots, Catalent's clinical supply services can handle a broad range of international compliance and distribution requirements to support global clinical trials. For further information on Catalent's Clinical Supply Services business visit https://www.clinical.catalent.com.

Catalent is a global leader in clinical supply services, with comprehensive and flexible solutions for small molecules, biologics, and cell and gene therapies and integrated solutions to accelerate speed to clinic. Catalent offers a full range services including clinical supply management, comprehensive packaging solutions, comparator sourcing, cold chain storage and global distribution and specialized supply chain services including direct-to-patient and demand-led supply. With nine GMP clinical packaging facilities and over 50 strategically located depots on six continents combined with more than 25 years' experience across thousands of studies in more than 80 countries, Catalent has the comprehensive services, global scale and expertise necessary to reliably supply clinical trials of all sizes and complexity anywhere in the world.

Calixar Invests in Pipeline of Highly Druggable Membrane Protein Targets & Native Antigens

Calixar recently announced its €1M ($1.2M) investment in a new pipeline of complex therapeutic targets and native antigens of high relevance for pharmaceutical companies. This strategic investment, supported by Bpifrance investment bank, will enable the company to be the exclusive provider and licensor for pharmaceutical companies, with the best native and functional membrane therapeutic targets (GPCRs, ion channels, transporters, receptors and viral targets). It will also help them to discover the best drugs (small molecules and conformational antibodies) and develop the best vaccines.

Drug development is becoming more costly and uncertain than ever (over $1bn – €0.9bn – in 2020, with a 95% failure rate). Only a few of the drugs authorized each year bring real health benefits. This is despite major scientific advances and ever-increasing investment, with over $150bn (€139bn) invested annually worldwide (source: EvaluatePharma).

Calixar was founded in 2011 with the aim of responding to those industry needs. It has developed its own unique technology, together with a research platform, in order to produce high-quality native membrane therapeutic targets that cover all therapeutic areas.

"Collective studies agree that the pharmaceutical industry needs to optimize its drug development model," said Emmanuel Dejean, founder and CEO of Calixar. "In Calixar's view, the problems faced in clinical development are related particularly to the unreliability of the therapeutic targets isolated upstream."

Membrane therapeutic targets (GPCRs, ion channels, transporters, etc.) are essential as templates in the development of drug candidates, both in small molecule screening and in the manufacture of therapeutic antibodies, or as antigens in the development of new vaccines. There is therefore a direct link between the quality of a therapeutic target and the reliability of the biodrug obtained downstream. Today, nearly all the available targets are obtained via denaturing purification and stabilization procedures, resulting in less than robust drug candidates and vaccines. This also partly explains the clinical phase failures and the poor performance of some drugs on the market.

There are several thousand therapeutic targets in humans, yet only a few of these are currently available to the pharmaceutical industry. To address this unmet medical need and industry gap, Calixar developed a technology enabling the development of very reliable native therapeutic targets that were previously unavailable; in order to improve the success rate of clinical studies and to open up new therapeutic pathways.

Calixar validated its technology with numerous clients and partners, from pharmaceutical and biotechnology companies to public and private research institutes. Its platform has been used to isolate over 100 client's targets involved in a number of diseases, many of which had previously never been subject to native and functional isolation. The recognized quality of Calixar's therapeutic targets led US biotech company Regeneron to enter into an initial exclusive licensing agreement with Calixar in 2019, for a major target.

CeQur Raises $115 Million to Support Commercialization & Scale-Up of Automated Manufacturing for CeQur Simplicity Wearable Insulin Delivery Device

CeQur recently announced the close of an oversubscribed $115-million equity financing. The company will use the funds to advance commercial plans for CeQur Simplicity, including market development activities, a phased commercial launch strategy that includes a limited market release in 2021, and the scale-up of high-volume manufacturing. CeQur Simplicity is both FDA cleared and CE-marked.

"We are grateful for the support from this group of world-class investors, who share our vision to transform the lives of people with diabetes who require daily insulin therapy. In the pilot launch of CeQur Simplicity, we've been very encouraged by the feedback from healthcare professionals, payers, and people with diabetes, which validates that this novel device offers meaningful benefits to a large segment of people who are insulin dependent," said Bradley Paddock, President and CEO at CeQur. "We look forward to advancing our commercial and manufacturing plans in preparation for our broadscale launch."

Currently, people with diabetes who require intensive insulin management utilize either multiple daily injections (MDI) or advanced insulin delivery devices. Research among individuals who manage their diabetes with MDI, and the medical professionals who treat them, demonstrates that many patients are not achieving their glucose targets in part due to lifestyle restrictions, social challenges, and fear of social stigma associated with insulin injections. For example, nearly two-thirds of patients studied do not feel comfortable injecting insulin in front of others. Additionally, healthcare professionals report that among the most challenging aspects of starting a patient on rapid-acting insulin are getting patients to perform multiple daily injections and the complex education required for patients. Given the challenges with current approaches to insulin injections and the global impact of diabetes, it is estimated that the potential market for simple insulin-delivery devices is approximately $7.5 billion in the US and roughly twice this amount globally.

"CeQur Simplicity offers a simple solution to a major barrier for many people who need mealtime insulin. This financing, which is transformative for CeQur, provides additional validation for the value of CeQur Simplicity as a simple, convenient and discreet bolus insulin-delivery device that is designed to address the burden of multiple daily injections for over 3 million Americans – and many more individuals around the world," said Richard Mott, Chairman of the Board at CeQur.

CeQur Simplicity is a simple, 3-day, wearable insulin device for discreet, convenient and injection-free bolus dosing. One Simplicity patch holds up to 200 units of rapid-acting insulin administered in two-unit increments and replaces, on average, nine mealtime injections over three days. Clinical research has shown that nearly 90% of patients using CeQur Simplicity reported following their insulin regimen better as compared to MDI. The device is clinically proven to improve glycemic control, with patients achieving significantly improved HbA1C and time-in-range (TIR) goals.

Akston Biosciences Launches Phase 1/2 Clinical Trial of Second-Generation COVID-19 Vaccine

Akston Biosciences Corporation recently announced the first participants have been dosed in an open-label trial of AKS-452, its COVID-19 vaccine candidate. The trial is managed by TRACER Europe B.V., a CRO specializing in fast-track clinical trials; and is being conducted at the University Medical Center Groningen (UMCG), one of the largest hospitals in the Netherlands. It will test both one- and two-dose regimens, each at three-dose levels.

The Phase 1/2 clinical trial, an open-label study, will evaluate 176 healthy volunteers between the ages of 18 and 65. Participants will receive one dose or two doses 28 days apart and the protocol will assess three-dose levels (22.5, 45, and 90 micrograms) to determine safety, tolerability, and immune response.

AKS-452 has demonstrated robust protection against infection in immunized non-human primates after challenge with the SARS-CoV-2 virus. Although intended to be refrigerated for long-term storage, it has been shown to be shelf-stable for at least 4 months at 25° Celsius (77° Fahrenheit) and maintains its potency for 1 month at 37° Celsius (95° Fahrenheit). The candidate does not include a live or weakened form of the virus, and has been engineered to use standard, low-cost, antibody manufacturing techniques, such that a single 2,000-liter production line could be capable of producing over one billion doses per year.

Based on Akston's proprietary Fc fusion protein platform, AKS-452 is a CoV-2 subunit vaccine designed to induce or boost a Th1/Th2 mixed immune response in patients against the Receptor Binding Domain (RBD) of the novel coronavirus spike protein. The Fc moiety aids in delivering the vaccine to antigen-presenting cells via binding to the Fc-γ receptor, and subsequent antigen processing and presentation to CD4+ T-cells. Directing the immune system against the RBD instead of the entire spike protein may be the most efficient way to prevent viral attachment and infection with minimal side effects. Furthermore, being the primary locus for infection, the RBD is highly conserved among mutated forms of the virus, and preclinical studies of AKS-452 have demonstrated robust antibody neutralization of the B.1.1.7 and B.1.351 variants.

"This is an important milestone in meeting the worldwide need for a next-generation vaccine against the SARS-CoV2 virus, one that is stable for months at ambient temperatures and can be quickly manufactured at very large scale," said Todd Zion, PhD, President & CEO of Akston Biosciences. "If proven safe and efficacious, AKS-452 promises to become an affordable and easily transportable vaccine that can speed the goal of achieving herd immunity, considering 93% of the world still has not been vaccinated. We believe that this is a vaccine for everywhere and everyone in the world."

2020 Global Drug Delivery & Formulation REPORT

Part Three of a Four-Part Series

Part 1: A Review of 2020 Product Approvals

Part 2: Notable Drug Delivery and Formulation Product Approvals of 2020

Part 3: Notable Drug Delivery & Formulation Transactions and Technologies of 2020

Part 4: The Drug Delivery and Formulation Pipeline

By: Kurt Sedo, Vice President Operations, and Esay Okutgen, Ph.D., Director Drug Delivery, PharmaCircle LLC

Introduction

There are only a limited number of plots or scales when it comes to movies and music. That is of course until something new is discovered and everyone quickly follows. It is much the same with drug delivery and formulation. Everyone was all in on oral sustained-release delivery and transdermals until the opportunities dried up. This was followed by injectables, notably longer-acting injectables. More recently, the drug delivery and formulation technologies that have captured the interest of pharmaceutical companies revolve around the use of injectables in the outpatient market. These technology shifts have largely arisen in response to the changing product opportunities presented with new molecular motifs and commercial realities. Transdermal and oral sustained release provided clinical and business opportunities for the large inventory of small molecule actives that could benefit from dose modification. Long-acting injectable technologies were a response to the emerging macromolecule and biologics sector. The development of more convenient injection technologies for outpatient use was less a response to a therapeutic challenge than a commercial opportunity. Office or hospital cased injections were not only more costly, but also inconvenient to providers and patients.

It seems that the latest evolution in pharmaceutical products is on par with the transition from small molecule oral therapeutics to macromolecules, proteins, and antibodies. The recognition that RNA represents a significant therapeutic motif has required the development of technologies that can effectively deliver these molecules to very particular cellular targets. At the same time, there is a growing confidence that gene and cell therapies can provide similar benefits with longer horizons. These new products also require effective and efficient drug delivery and formulation technologies to ensure efficacy, safety, and stability.

In terms of transactions, while the numbers jumped in 2020, the deals largely used the same commercial templates as in previous decades. An exception might be the increasing number of deals announced that involve companies selling future milestone and royalty revenues in exchange for upfront cash. Drug delivery and formulation technologies in 2020 were a mix of the old and new, and their importance was reinforced. As we saw in 2020, even something as seemingly trivial as relaxing storage and transportation temperatures or larger vial sizes can make a big difference in terms of impacting a global pandemic.

2010s Technologies of the Decade - Subcutaneous Injectables

If the 1980s through 1990s were the decades of transdermal and extended- release oral technologies, and the 1990s through 2000s were the decades of PEGylation and injectable depot technologies, we can with some confidence declare the 2010s the decade of subcutaneous injectable technologies.

With the development and approval of a wide range of biologics possessing intrinsic long-acting properties, the therapeutic and commercial opportunity that quickly became apparent was making these therapeutics more convenient for patients and the healthcare system. Biologics can generally be readily administered without much complexity using an intravenous route of delivery. Too often, this requires in-patient administration that can demand hours-long infusions with complex dose ramping. Moving these often chronically administered biologics to out-patient use requires rerigging the products, preferably with limited formulation adjustments to simplify regulatory requirements and to reduce any chance of a clinical surprise.

The solution began to appear in the 2000s with the development of subcutaneous injection devices that not only simplified out-patient dosing with single-dose injectors, but also removed the intimidation of a typical needle. The opportunity that largely pushed this development was the increasing use of insulin for the treatment of Type 2 diabetes. While patients with Type 1 diabetes had long resigned themselves to drawing up a dose and injecting subcutaneously for the rest of their lives, Type 2 patients were intimidated by the process of doing dose calculations and going through the injection process.

These single and multidose injectors were soon adopted for low-volume biologicals that required injection as often as daily or as infrequently as monthly. These injectors not only met a pressing therapeutic need, but also accelerated the adoption of these biological products in the out-patient setting. Products like AbbVie's Humira and Amgen's Enbrel have managed to achieve multibillion dollar annual sales even though they require patient self-injection.

Despite the acceptance of these devices, there remained a significant therapeutic gap and commercial opportunity. These pen devices were generally limited to the injection of relatively small volumes, on the order of 1 ml or less. This limited the opportunities for products that required larger volumes for a variety of reasons, including stability and viscosity. The prospect of multiple individual doses was not an appealing option.

The solution to this challenge was provided by Halozyme and their Enhanze technology, a drug delivery system that uses high-dose recombinant human hyaluronidase PH20 enzyme (rHuPH20) co-administered subcutaneously along with the therapeutic, either sequentially or with co-formulation. The enzyme degrades hyaluronan [sodium hyaluronate or hyaluronic acid (HA)], a polysaccharide found within the extracellular matrix. Degradation of hyaluronan at the local injection area allows dispersion and absorption of the therapeutic agent more easily and rapidly and is restored via normal processes within 24-48 hours. The Enhanze technology permits large- volume administration, 2-20-ml subcutaneous injections, and up to 600-ml subcutaneous infusion.

Notable approved products utilizing Enhanze include:

- Genentech (Roche) - Herceptin SC/Herceptin Hylecta
- Biogen / Roche - Rituxan Hycela/MAbThera
- Baxalta (Takeda Pharmaceutical) - HyQvia
- Genentech (Roche) - Phesgo FDC
- Janssen / Genmab - Darzalex FASPRO

Surprisingly, for the better part of a decade, Halozyme has been the sole provider of high-volume subcutaneous formulation technology. Year after year, Halozyme has been signing deals with new and existing partners to extend the use of the Enhanze technology, but there may be some competition in the wings with Arecor's Arestat technology.

If the 1980s and 1990s were defined by transdermal and long-acting oral technologies, the 1990s and 2000s by PEGylation and long-acting injectable depot technologies, and the past decade by subcutaneous injection devices and technologies, what comes next? The early favorites are gene and cell technologies along with RNA delivery technologies.

Notable Drug Delivery and Formulation Technologies of 2020

Technology: NAV Technology Platform
Most Advanced Stage: Marketed
Technology Category(s): Adeno-Associated Virus Vectors
Company: REGENXBIO
Notable Pipeline: Zolgensma (SMA, Marketed, Novartis), RGX-314 (Wet AMD, Phase 2)
Notable: A foundational technology for gene delivery.
Technology Summary: The NAV Technology Platform consists of over 100 novel adeno-associated virus (AAV) vectors, including AAV7, AAV8, AAV9, AAVhu68 (AAV9 variant), and AAVrh10 (NAV Vectors), applicable to the delivery of genetic materials to targeted cells. Inside the cell nucleus, the NAV capsids dissolve and release a gene that is transcribed into RNA and encoded into the desired protein. NAV Technology provides advantages beyond "traditional" AAV, including more efficient delivery, a quicker onset of gene expression, higher tissue selectivity, and high titer manufacturing.

Technology: Clearside SCS Microinjection Platform
Most Advanced Stage: Registration
Technology Category(s): Ocular Delivery Devices/Dispensers, Specialty Syringes, Poration, Microneedles, Low-Dose Formulations
Company: Clearside Biomedical
Notable Pipeline: Xipere (Macular Edema, Registration, Bausch), CLSAX (Wet AMD, Phase 1/2)
Notable: A new administration site for the treatment of ocular diseases.
Technology Summary: The technology uses a hollow microneedle to deliver drugs via controlled infusion directly to the suprachoroidal space (SCS, space between the sclera and choroid), which has only been accessible through surgical techniques. There is no limitation on the types of drugs that can be administered with the technology. Administration can be targeted to the posterior region to permit flow circumferentially toward the retinochoroidal tissue, macula, and optic nerve in the posterior segment of the eye. Particle size is critical as 20-nm particles readily spread in the SCS and within the sclera, while 1000-nm particles are retained primarily in the SCS.

Technology: TransCon - Transient Conjugation
Most Advanced Stage: Registration
Technology Category(s): Conjugates, PEG Polymer
Company: Ascendis Pharma
Notable Pipeline: TransCon hGH (Growth Disorder, Registration), TransCon PTH (Hypoparathyroidism, Phase 3)
Notable: A technology that may improve upon, and expand the applicability of, PEGylation.
Technology Summary: TransCon molecules have three components: an unmodified parent drug, an inert carrier, and a releasable linker. When linked, the carrier inactivates and shields the parent drug from clearance. After administration, the physiologic pH and temperature conditions initiate the release of the active, unmodified parent drug in a predictable release manner. Because the parent drug is released unmodified with no residual linker, it retains its native activity. The technology can use linear, branched, and multi-arm PEG (TransCon PEG). The TransCon technology can be applied broadly to proteins, peptides, and small molecules. The reversible linker chemistries are designed to provide predictable rates of autohydrolysis in vivo.

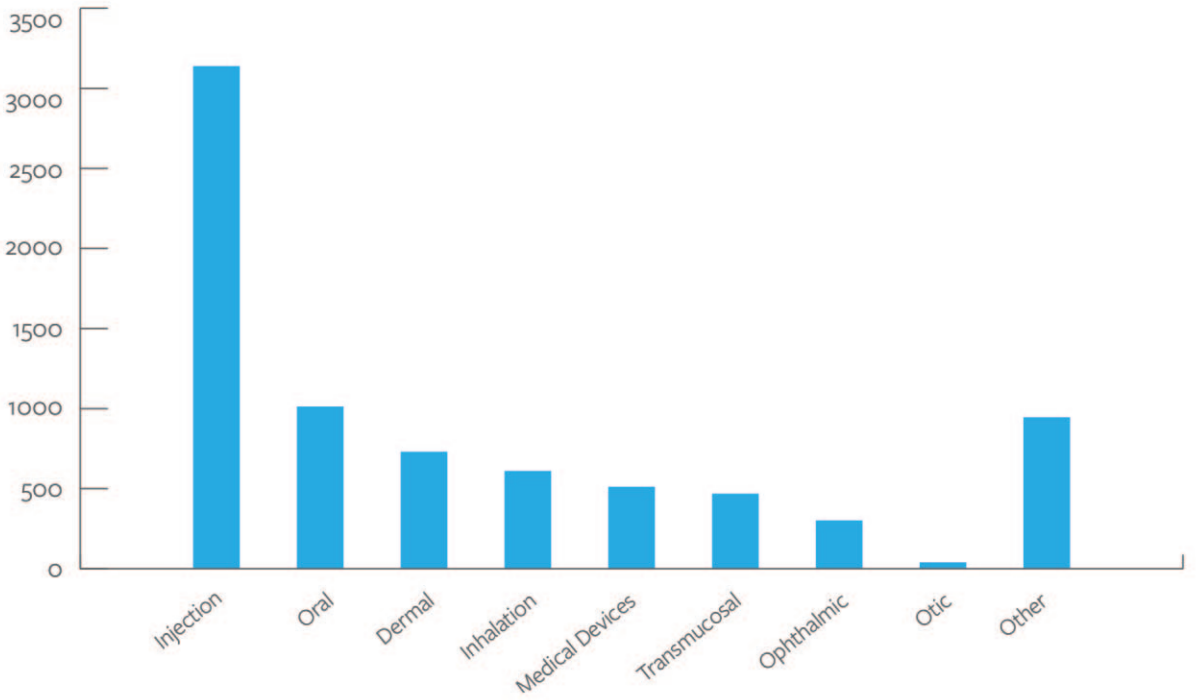
Technology: BEPO
Most Advanced Stage: Phase 3
Technology Category(s): Biodegradable Gel/Suspension
Company: MedinCell
Notable Pipeline: mdc-IRM (Schizophrenia, Phase 3, Teva), mdc-CWM (Pain Inflammation, Phase 2, Arthritis Innovation Corp.)
Notable: Perhaps the next-generation PLGA-based depot technology.
Technology Summary: A PLA/PEG/PLA based in-situ forming hydrogel depot system composed of a mono-dispersed network of hydrophilic chains (PEG) linked with hydrophobic micro-domains (PLA), which can entrap hydrophilic macromolecules. The hydrophobic micro-domains are able to solubilize and retain hydrophobic substances. Ten day to six-month release of small molecules and one-week release of peptides have been demonstrated.

Technology: Arestat
Most Advanced Stage: Phase 1
Technology Category(s): Stabilization Technologies, Concentrated Suspension/Viscous Solution, Rapid Acting Injectables
Company: Arecor
Notable Pipeline: AT247 (Diabetes, Phase 1), AT278 (Diabetes, Phase 1)
Notable: A potential alternative to Halozyme's Enhanze for larger volume subcutaneous injections.
Technology Summary: The Arecor technology provides the stabilization of proteins/biologics when stored under non-refrigerated conditions, even during storage at elevated temperatures and in higher concentrations for 12 months or longer. Arestat reduces the viscosity of biologic formulations, enabling higher concentration doses in easy-to-administer formats. It also enables liquid-stable versions of live-virus containing products that are used in vaccine and gene therapy products in liquid presentations at usual cold chain temperatures. The technology's lead products AT247 and AT278 provide an ultra-rapid onset of action of insulin while ensuring product stability.

Technology: MIMIX
Most Advanced Stage: Preclinical
Technology Category(s): Poration, Dissolvable Microneedle, Solid Dose Injectors, Biodegradable Non-PLGA Microcaps/Implants
Company: Vaxess Technologies
Notable Pipeline: Flu Vaccine (Preclinical), COVID-19 Vaccine (Preclinical)
Notable: A potentially improved delivery system for vaccine delivery.
Technology Summary: A microneedle patch incorporating silk fibroin-based biomaterials as a controlled-release depot tip on the dissolvable microneedle. The shelf-stable, easy-to-apply, patch enables the adjustable delivery of actives from small molecules to biologics. The needle base dissolves in minutes, embedding the slow-release tips that continue to deliver drugs into the skin for minutes to months.

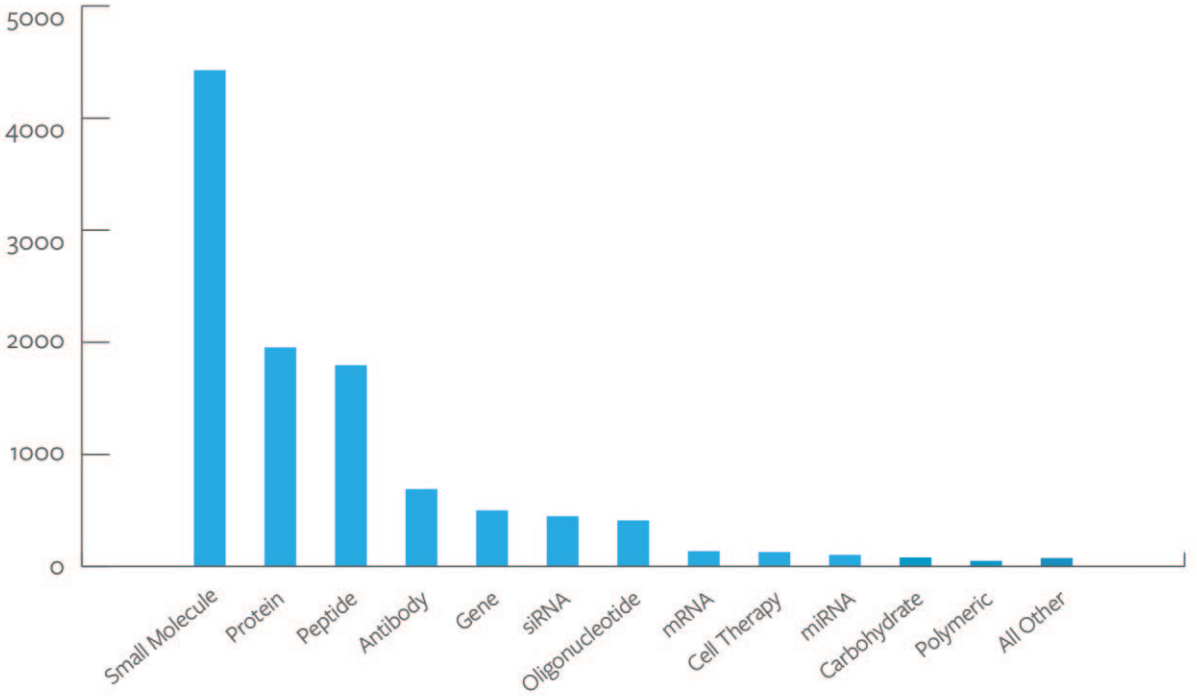
Injection and Small Molecules Continue to Dominate Technology Development Activities

Active Technologies by Delivery Route



Source: PharmaCircle Drug Delivery Technology Analyzer Module March 31, 2021

Active Technologies by Molecule Type



Source: PharmaCircle Drug Delivery Technology Analyzer Module March 31, 2021

Table notes: Technology assignments are made by PharmaCircle analysts. Only technologies identified as currently active are included. Technologies can be applicable to more than one Route and Molecule Type. All other includes a variety of technologies and routes not easily assignable to a category.

Drug Delivery and Formulation-Related Transactions Trends of 2020

While there will always be a debate regarding what exactly is drug delivery and formulation in the 21st Century, for this review, we take a broad view of the subject. From this perspective and in the context of where companies put their money in 2020 when it came to technology, there were two obvious areas of investment.

Gene Therapy

Both gene and cell therapy have yet to properly reward the companies that have invested in the platforms, technologies, and products. This may of course just be the calm before the storm that was seen with antibody therapies. An initial sense of optimism in the potential of antibodies that was seen in the late 1980s and early 1990s was largely squashed with a relative lack of meaningful products along with issues related to the humanization of antibodies and identifying therapeutic targets. For the faithful, validation and success arrived shortly thereafter.

Gene and cell therapy had its own moment of enthusiasm in the mid-1990s that was squashed by a fatal reaction to an adenoviral gene therapy. At the same time, the costs of both gene and cell therapy were an order of magnitude greater than what the market was willing to bear. Following a reworking of gene therapy vectors to address safety issues and the evolution of a marketplace that is now willing to accept million-dollar pharmaceutical products, it seems that gene and cell therapy is prepared to explode with a variety of products addressing challenging medical indications. But, after a crop of initial approvals over the past three years, certain realities have started to emerge. This seems to represent the same calm that was seen with antibody therapies. Having learned their lesson, or perhaps being afraid to miss the next wave, many companies chose to invest heavily in both gene and cell therapy in 2020. Some notable transactions include the following:

- 2020-12 Bayer and Asklepios, Alzheimer's, Parkinson's, USD 4 billion
- 2020-10 Roche and Dyno Therapeutics, CNS, Liver, USD 1.8 billion
- 2020-04 Vertex and Affinia, Cystic Fibrosis, CNS, USD 1.6 billion

RNA Therapeutics and Vaccines

The other theme of 2020 was an interest in the foundational technologies necessary to deliver the RNA therapies that captured the world's attention in 2020 with the conditional approvals of the Pfizer/BioNTech and Moderna COVID-19 vaccines. This followed on approvals in 2018, 2019, and 2020 of siRNA therapeutics from Alnylam. With clear evidence that RNA therapeutics are real, there has been renewed interest in accessing the necessary delivery technologies for RNA and oligonucleotides. Notable transactions in 2020 include the following:

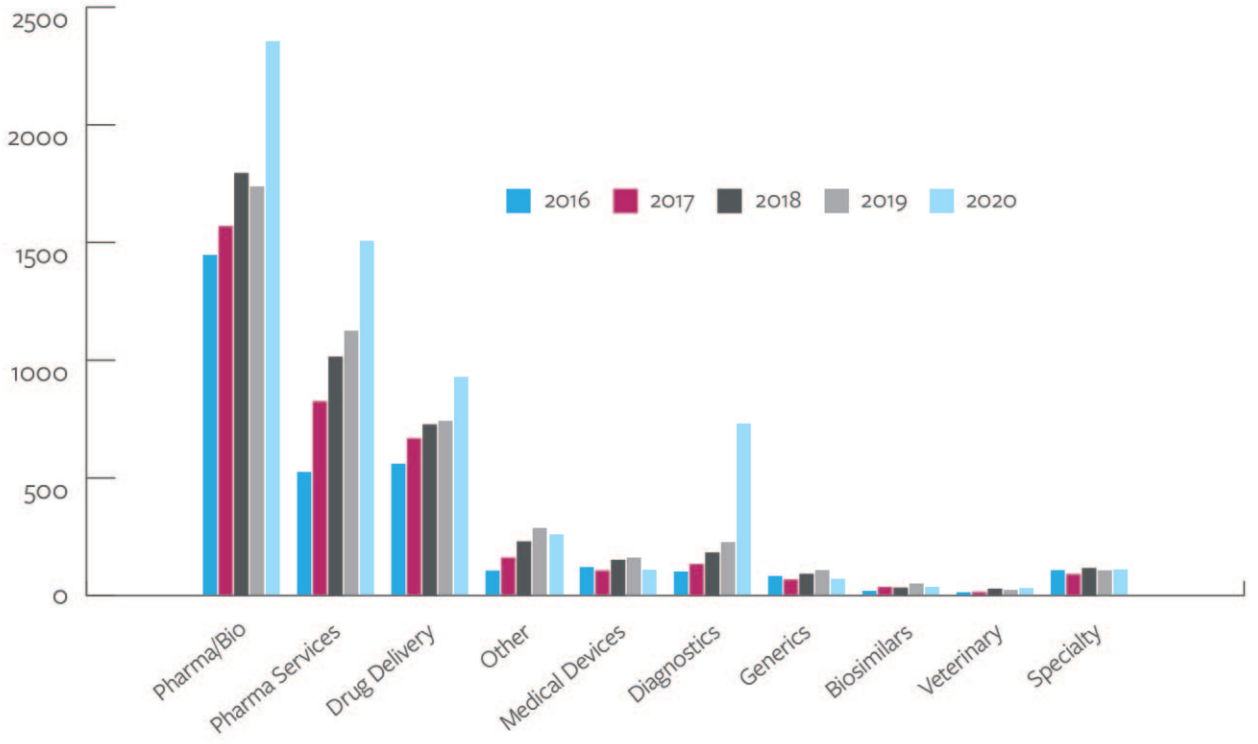
- 2020-06 Sanofi and Translate Bio, Cystic Fibrosis, Infections, USD 1.9 billion
- 2020-01 Ionis and Aro Biotherapeutics, Cancers, USD 1.4 billion
- 2020-06 Lilly and Evox Therapeutics, CNS, USD 1.2 billion
- 2020-09 Chiesi and Moderna, Pulmonary Arterial Hypertension, Cancer, USD 425 million

There were many other drug delivery and formulation-related transactions that included company acquisitions, Gilead and Immunomedics (USD 21 billion), Novo Nordisk and Emisphere (USD 1.4 billion), as well as product and technology acquisitions. Totaled up, these drug delivery and formulation deals exceeded $80 billion in 2020, at least in the usual "Biobuck" currency that always includes performance-related milestone payments.

A focused overview of 2020 transactions by business sector and transaction type are presented in the following charts. In general, transactions experienced a considerable jump in 2020 relative to previous years.

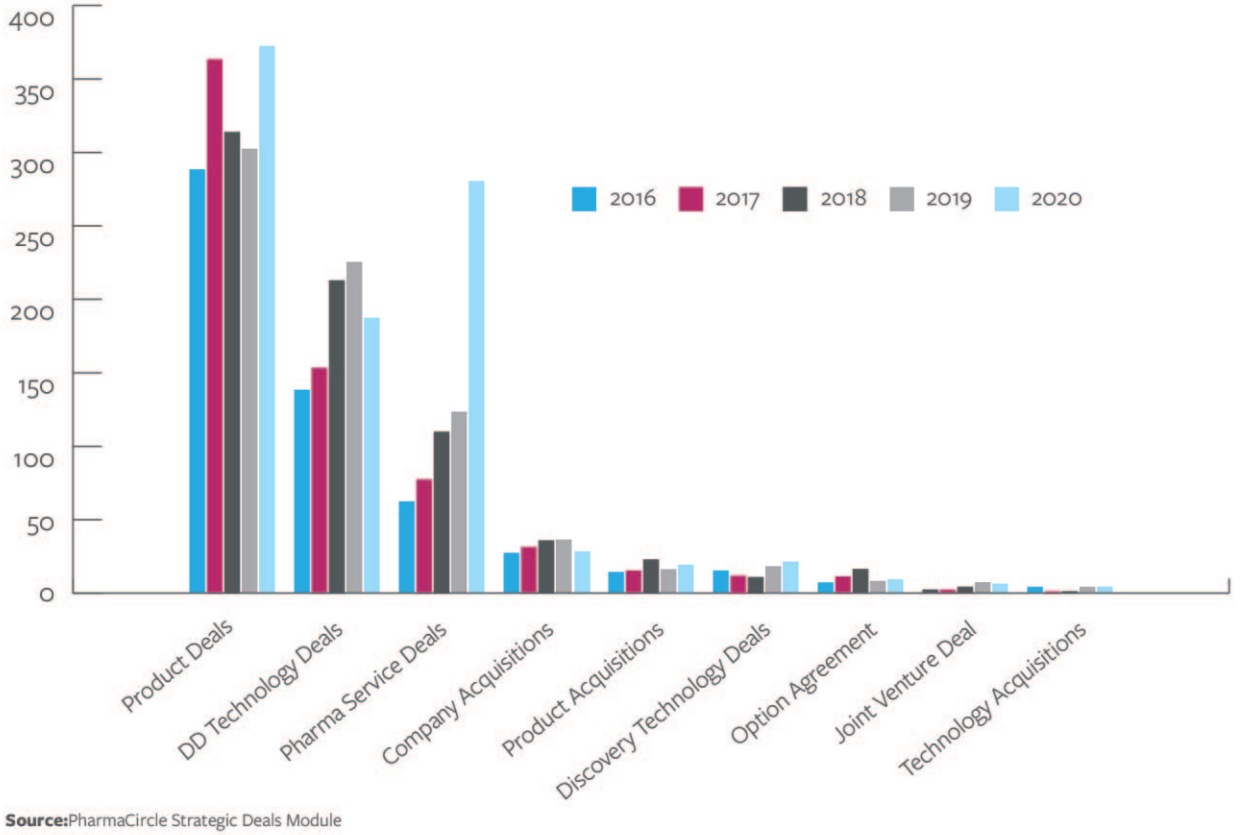
Transactions in the Pharma Sector Jumped Significantly in 2020, Notably Product and Pharma Service Deals

Pharma-Related Transactions by Category (2016-2020)



Source: PharmaCircle Strategic Deals Module

Drug Delivery Transactions by Transaction Type (2016-2020)



Source: PharmaCircle Strategic Deals Module

Table notes: Transaction assignments are made by PharmaCircle analysts. The transaction numbers include amendment and termination agreements which can account for 10%-15% of all transactions.

VITAL Dose®
Controlled Release Excipient

Sustained Drug Delivery

Enabling Technology Platform
Patient-Centric Therapeutics

VitalDose® EVA is a copolymer drug-delivery platform providing controlled release through implant and insert dosage forms. Whether the challenge relates to a new molecular entity and new target, or an opportunity in life cycle management, our scientists and engineers will partner with you to create novel drug-products.

- Biologics and small molecules
- High drug loading capacity
- Variety of geometries
- Local or systemic administration
- Long clinical use history
- Established regulatory path

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The chemistry inside innovation™

Formulation Forum

Considerations in Formulation Development of Injectable Solutions

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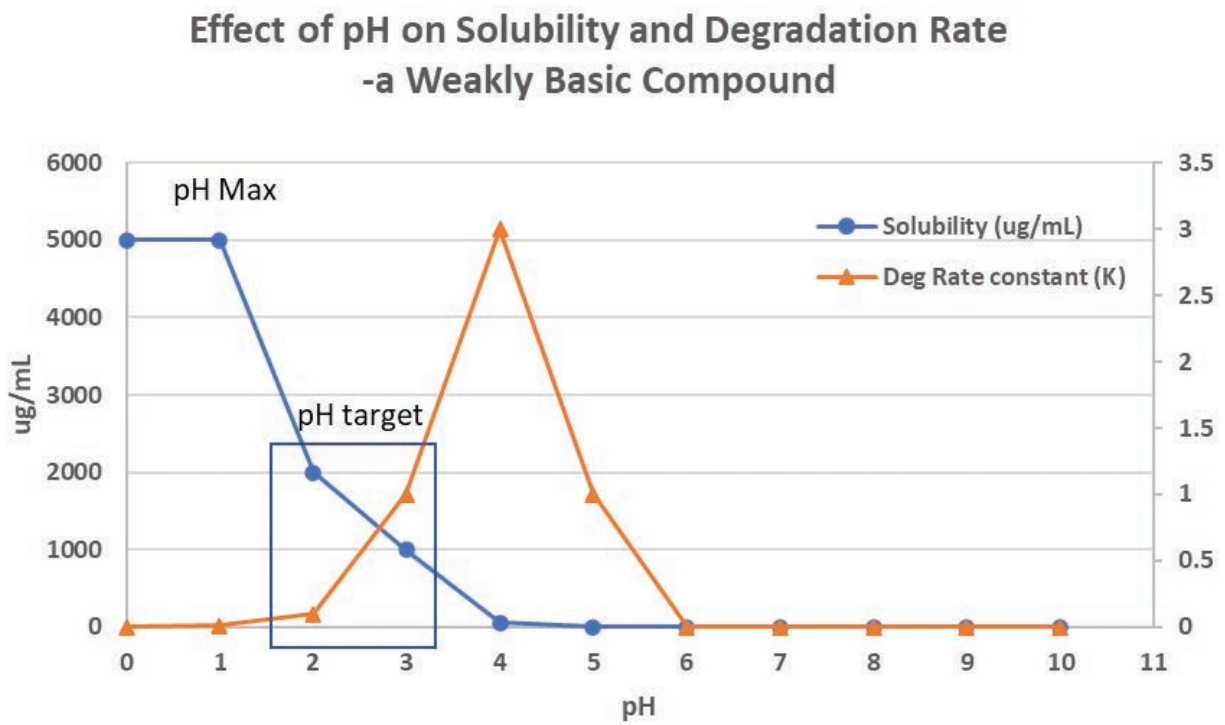
INTRODUCTION

Injectable solutions are intended for administration to the human body by intravenous, intramuscular, or subcutaneous injection. Advantages of injectables include fast onset, and other parent routes of administration, reproducible PK/efficacy profile, high bioavailability as a result of bypassing the oral absorption barrier, and suitability of administration under hospital setting. In order to meet the safety, efficacy, and quality standards of parenteral dosage forms, injectable solutions have to be sterile, low pyrogen, and meet the requirements of compendia specifications, such as >90% label claim, related substance level lower than the tox qualified level, content uniformity, pH, osmolality, particulate matter, essentially free of visual foreign matter, etc.

The main challenges of parenteral dosage forms are achievement of formulation stability, compatibility of drug substance with packaging components, and sufficient drug concentration within a reasonable pH range and without using excipient levels that causes blood incompatibility and tissue irritation

FIGURE 1



A guide in selection of a target solution pH by balancing solubility and stability.

"The main challenges of parenteral dosage forms are achievement of formulation stability, compatibility of drug substance with packaging components, and sufficient drug concentration within a reasonable pH range and without using excipient levels that causes blood incompatibility and tissue irritation issues. Those requirements necessitate a comprehensive characterization of drug substance physiochemically."

issues. Those requirements necessitate a comprehensive characterization of drug substance physiochemically. In addition, the critical manufacturing processing conditions of injectable liquids have to be evaluated and stringently controlled in order to meet requirements for assay/related substance, CU, leachable/extractables, sterility, pyrogen, and particulate matter specifications.

The process of parenteral formulation development can be divided into preformulation studies, prototype formulation development, accelerated stability studies, packaging selection, process development to evaluate critical process parameters, scale-up, manufacturing of demonstration and GMP baches, and their long-term stability studies for up to 24-36 months.

PREFORMULATION

Preformulation studies are critical for injectable solution development, which covers the measurement of solubility/stability as a function of pH, pKa, partition, moisture sorption/desorption, polymorphism and crystallinity by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and powder X-ray diffraction, salt form screening, stability of drug substance, assessing the compatibility of API and excipients using stress testing, and forced degradation to evaluate the effect of pH, temperature, humidity, light, and oxidizing agents. In addition, compound solubility in commonly used solvent, cosolvent, surfactant, solubilizer, and complex agents will be useful in setting the direction of formulation development.

The aqueous solubility of a compound is dependent on its state of ionization, including the ratio of ionized to unionized fraction. The degree of ionization can be estimated using the Henderson–Hasselbach equation. For weak acidic compounds, (HA) is:

$$pH = pKa + \log[A^-]/[HA];$$

for weakly basic compounds, (BH) is:

$$pH = pKa + \log[B]/[BH^+],$$

where K_a is the ionization constant of the dissociation constant.

Effect of pH on API solubility and stability is most important for solution formulation development of ionizable compounds, which will guide the selection of formulation pH in the solution dosage form (Figure 1). Salt or co-crystal form is another factor that may also affect the compound solution solubility; salt form screen or in-situ salt formation should be evaluated to find a salt form that enhances compound solubility.

FORMULATION DEVELOPMENT

Prototype formulation development covers selection of buffer, pH, stabilizers, isotonicity agents, antioxidants, preservatives, and solubility and/or viscosity-enhancing agents.

pH & Buffer Selection

The pH is one of the critical aspects of parenteral formulation, which should have a target pH as much as possible close to physiological pH. An ionizable compound can be solubilized to the desired concentration by pH adjustment. The acceptable range is pH 2–11 for intravenous and intramuscular injection and pH 4-9 for subcutaneously injection due to potential irritation issue. The solution pH can be controlled by a buffer, such as acetate, phosphate, citrate, histidine, TRIS, and others, to an ideal range of pH 5-8. The buffer capacity should be kept to a minimum to enable body fluid to adjust the formulation pH quickly to physiological pH; otherwise, an irritation at the injection site may be present. For IV infusion, the solution pH is typically controlled by the salt form of the drug or by acids and bases without buffer due to in vivo tolerability considerations. In some cases, a compromise may be required between solubility and stability of the drug substance in

order to find a target formulation pH in which both drug loading and product stability are acceptable (Figure 1).

Osmolarity

Parenteral formulations should be ideally isotonic whenever possible. Dextrose, Mannitol, glycerol, and sodium chloride are the most commonly used agents to adjust the tonicity of a solution formulation. Hypertonic solutions will cause blood cell deformation, whereas a hypotonic solution will lead to rupture of blood cell that results in hemolysis. Formulations with an osmotic value in the range of 250 to 350 mOsm are acceptable; any exception to this range should be justified case by case. For example, for formulation containing solvents, such as ethanol, even though the measured osmolality is high for those formulations, because the small solute can permeate through blood cell membranes rapidly to reach equilibrium inside and outside of the cell membrane, high osmolality value may not proportionally impact on tonicity *in vivo*.

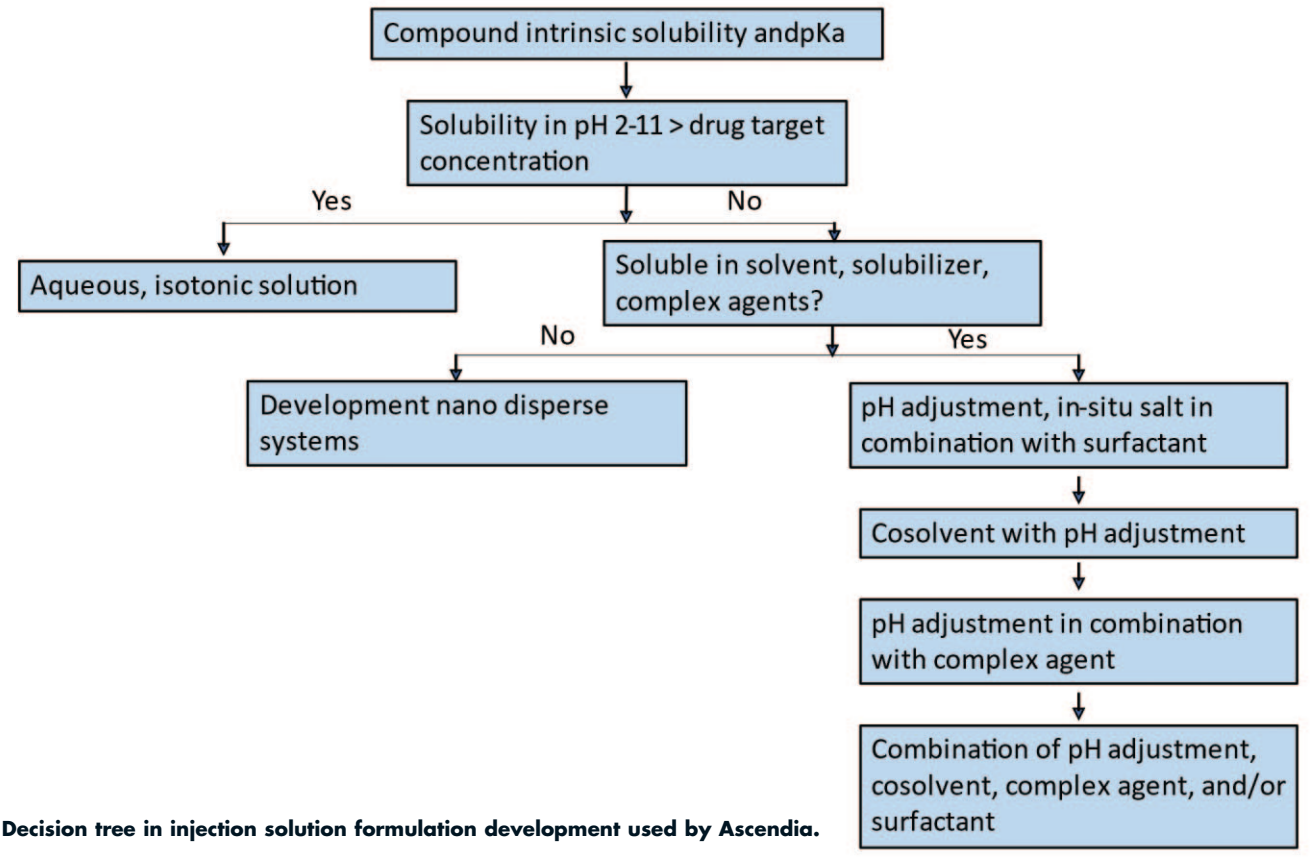
Solubilizers

Due to the high percentage of insoluble compounds in the development stage, solubilization becomes an important task for pharmaceutical scientists in their daily works. In addition to alteration of pH and in situ salt formation, solubilizers, such as surfactant, solvent, co-solvent, complexing agents, or their combinations, are routinely utilized to solubilize poorly water-soluble compounds. Co-solvents are used when a drug substance has insufficient solubility in a simple aqueous or pH-adjusted vehicle. The water-soluble organic solvents and surfactants used in marketed injectables include propylene glycol, polyethylene glycol 300/400, glycerin, ethanol, polysorbate 80, Cremophor EL, N-methyl-2-pyrrolidone (NMP), etc. These solvents are usually used in combinations with each other with an aid of pH adjustment. A decision tree can be used as a guide for the injectable solution development (Figure 2).

Container & Closure

Compatibility of injectable solution with stopper and container is another critical aspect for injectable formulation development. For high solvent/surfactant content formulations, assessment of potential discoloring, deformation, and leachable of the stopper as a result of incompatibility should be evaluated as soon as the prototype formulation is selected. For early formulations, a Teflon- coated stopper is usually used to shorten the development timeline to avoid any potential compatibility issues. Leaching of alkaline materials from glass may cause an increase in solution pH, which could be significant for un-buffered formulations, wherein the compound's solubility

FIGURE 2



Decision tree in injection solution formulation development used by Ascendia.

and stability are sensitive to the pH change. Container-closure integrity should be evaluated for each injectable solution product during development prior to manufacturing and during stability study to ensure integrity of injectable products is maintained.

PROCESS DEVELOPMENT & SCALE-UP

Process development is centered around three of the most critical areas for sterile products: sterility, stability, and particulate matter. Parenteral manufacturing requires filling and sealing to be carried out in a Class 100 environment for injectables processed under aseptic conditions, the manufacturing process of which should be validated using media runs to ensure sterility of the finished dosage forms. For terminal sterilized products, they can be manufactured in Class 10,000 environment, which however, requires sterilization cycle validation that ensures 6-log reduction of bioburden. Critical process parameters that affect product potency and stability, such as light, bulk holding, filter compatibility, tubing selection, nitrogen protection, etc should also be evaluated during process development and scale up.

IN VITRO EVALUATION OF INJECTABLE SOLUTIONS

Compatibility With Infusion Sets

IV formulations are typically injected by syringe and administered using infusion sets. Evaluations should be undertaken to evaluate if the compound is absorbed into the syringe and infusion set. Studies should show that no significant losses occur following filtration, injection, or infusion under the conditions of administration.

TABLE 1

Development Stage	Minimum Shelf-Life
GLP Tox	2-4 weeks
Phase 1	3-6 months
Phase 2	12 months
Phase 3	18 months

Recommended minimum shelf-life at different stages of development.

Plasma & Blood Compatibility

Compounds to be administered intravenously must be compatible with plasma and blood. Evaluation of the compounds in lead formulations should be undertaken initially in the blood and plasma of relevant preclinical species.

Plasma precipitation may result in embolism and subsequent death. A plasma precipitation test should be conducted to reduce the risk of embolism during in vivo studies. The study can be conducted by diluting the formulation with control plasma and observe for signs of precipitation. If precipitation is evident, an alternative formulation should be sought to avoid the precipitation or the concentration of the compound in the formulation should be lowered to prevent plasma precipitation.

The compound in the formulation should not cause hemolysis, significant crenellation, or erythrocyte clumping. There should also be no adverse reactions, such as thrombophlebitis, observed at the injection site following IV administration. A further evaluation in human blood and plasma should be undertaken in the formulation of choice for clinical trials.

Formulation Stability

A minimum storage life of 18 months, preferably at room temperature, is desired for a commercial parenteral solution formulation. If sufficient solution stability cannot be obtained by storing at room temperature, refrigerated storage at 2°C -8°C or at -20oC may be considered. Solution stability studies should be undertaken to predict storage life under both conditions. It is expected that an ideal injectable solution will demonstrate suitable stability in solution over the target storage life period. However, when adequate solution stability cannot be obtained, the development of a lyophilized product should be considered. The recommended minimum shelf-life is different at various stages of development. Table 1 summarizes the minimum recommended shelf-life at different stage of development.

SUMMARY

Injectable solutions offer an attractive alternative to oral dosage form due to fast onset, reproducible PK/efficacy profile, high bioavailability as a result of bypassing the oral absorption barrier, and suitability of administration under hospital setting. The main challenges of parenteral dosage forms are achievement of formulation stability, solubility, sterility, and reduction of blood incompatibility and tissue irritation issues. Formulation development of injectable solution can be divided into preformulation studies, prototype formulation development, accelerated stability studies, packaging selection, process development to evaluate critical process parameters, scale-up, manufacturing of demonstration and GMP baches, and long-term stability studies. ◆

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DRY-POWDER THERAPEUTICS

Respiration Inspiration: Local Treatment of Lung Cancer by Dry-Powder Inhaler

By: Philip Kuehl, PhD, and Kimberly B. Shepard, PhD

CHALLENGES IN LUNG CANCER TREATMENT

As of 2017, lung cancer was the leading cause of cancer-related deaths in Americans, with non-small-cell lung cancer (NSCLC) making up the majority of cases.[1] Despite dozens of approved treatments for lung cancer, survival rates for advanced cases remain poor. One study found only one-third of Stage IV patients in a particular cohort remained alive and progression-free after 12 months of treatment.[2] Overall, fewer than 5% of Stage IV patients survive for 5 years, despite intensive treatment with chemotherapy.[3] Immunotherapy combination treatments can increase progression-free survival by up to 4 months.[4]

Effective lung cancer treatment faces two challenges. The first is the toxicity and/or side effects associated with systemic administration. Most lung cancer treatments are administered systemically, whether by injection, intravenous infusion, or the oral route. For example, chemotherapy-based treatments and large-molecule biologics for immunotherapy are administered by intravenous infusions and can be poorly tolerated by patients. The blood drug levels required for adequate lung tissue exposure are high enough that adverse effects are common.[3,5] Many approved anticancer compounds are highly potent, but are rarely used due to severe toxicity. A second challenge to effective lung cancer treatment is the method of administration. Treatment by intravenous infusion must occur in a clinical setting, leading to high costs and challenges in patient compliance. For lung cancer, local delivery may provide a solution.

Site-specific (ie, local) treatment of lung cancer using an inhaled formulation offers an ideal means to overcome both of these challenges. The disadvantages of systemic administration can be overcome through local delivery using such well-established devices as dry-powder inhalers (DPIs), metered-dose inhalers, or nebulizers. There is a long history of treating lung ailments by such devices. DPIs are often preferred, due to their ease of use and product stability at ambient conditions. Issues with treatment convenience and compliance are also overcome with these devices, as patients can self-administer therapeutics at home. This is especially advantageous because lung cancer therapeutics, particularly immunotherapies, are often administered indefinitely as maintenance treatments.

The following describes the formulation and manufacturing considerations for development of dry-powder therapeutics for local treatment of lung cancer. Two case studies are presented in which two approved drugs — 5-azacytidine (5AZA) and topotecan — are successfully formulated for DPI administration to the lung.

FORMULATION & MANUFACTURING CONSIDERATIONS

To deliver any drug by inhalation, particle size is critical. The aerodynamic diameter of an aerosol particle, whether a solid for delivery by a DPI or liquid for delivery by a nebulizer, determines where the particles end up in the respiratory tract. For spherical particles, the aerodynamic diameter is a simple function of its geometric diameter and density (see equation 1):

Equation 1

$$d_a = d_g \sqrt{\rho_P / \rho^*}$$

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where d_a is the aerodynamic diameter, d_g is the geometric diameter, ρ_P is the density of the particle, and ρ^* is the reference density of 1000 kg/m^3.[6]

Particles that are too large (those with aerodynamic diameters larger than about 5 microns) tend to get stuck at the back of the throat, failing to follow inhaled air around the 90-degree bend in the throat from mouth to trachea. Particles that are too small (below about 1 micron) fail to deposit in the lung and are exhaled out of the body. For optimum deposition of drug in the deep lung (that is, bronchioles and alveoli), aerosol particles with aerodynamic diameters of 1 to 5 microns are desired.[6]

In liquid-based delivery systems (nebulizer formulations), droplet size is controlled by an atomizer and compressed air. For solid-based delivery systems (formulations for DPIs), particle engineering is needed to achieve the target size distribution for pulmonary delivery. Micronization, often performed using a jet mill, can reduce the particle size of the active pharmaceutical ingredient (API) to the correct range. The API particles are then blended with a carrier, such as lactose, to prevent reaggregation of the micronized material.

Spray drying offers another flexible approach to create dry-powder particles with the correct size for inhalation. In this process, API and excipients are co-dissolved in a solvent and atomized into droplets, which are introduced into a drying chamber. Contact with hot drying gas rapidly removes solvent from the droplets, creating solid particles. The spray-dried dispersion (SDD) particles are separated from the outlet gas stream using a cyclone collector. By carefully tuning the droplet atomization and drying process parameters, an inhalation-ready powder can be manufactured. Some common spray-drying inhalation excipients include stabilizing sugars, such as trehalose, mannitol, and lactose, as well as the amino acid L-leucine. L-leucine is used in inhalation formulations to form a crystalline shell on the outside of particles, acting as a dispersant to improve aerosol performance.[6] Further, we describe the successful use of spray-drying to prepare formulations for inhaled delivery.

CASE STUDY 1: 5-AZACYTIDINE

The first case study describes the preparation of a dry-powder 5AZA SDD for local inhaled delivery to the lung. The pharmacokinetic performance and efficacy of the SDD is compared to those of an inhaled aqueous formulation and an injectable systemic formulation.

5AZA is a chemotherapeutic that helps reduce the growth of cancer cells by inhibiting DNA methylation, a critical process in cell replication. The drug is currently approved for treatment via injection for myelodysplastic syndromes and leukemia and is in clinical trials for treatment of other cancers. When administered systemically, dose-limiting toxicity is often observed, which limits the compound's effectiveness. 5AZA is an excellent candidate for local delivery to the lung because pulmonary delivery will reduce toxicity and minimize the effects of 5AZA on the DNA of healthy tissue.

Formulation & *In Vitro* Characterization

Spray drying was used to produce dry-powder SDD particles that contained 10% 5AZA, 70% trehalose, and 20% L-leucine by weight. X-ray diffraction showed that the L-leucine was crystalline, and thermal analysis showed a single amorphous trehalose/5AZA phase. The mass median aerodynamic diameter (MMAD) of the 5AZA SDD was measured with a Next Generation Impactor™ (NGI) and a Plastiape low-resistance DPI device. The measured value of 3.6 +/– 1.6 microns was within the target range for delivery to the deep lung.

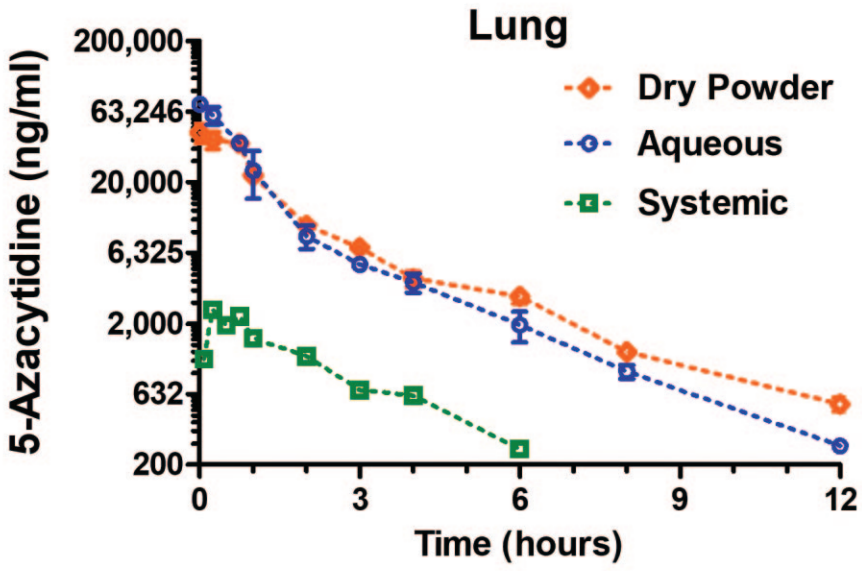
Manufacturing Approach

The greatest challenge in developing a 5AZA SDD was the poor chemical stability of 5AZA in water. 5AZA is easily dissolved in dimethyl sulfoxide (DMSO), but trehalose and L-leucine are not adequately soluble in DMSO for a single-solvent approach to be feasible. To combat this issue, a "solvent-shift" spray-drying process was used, in which an aqueous solution of trehalose and L-leucine was prepared and then combined with the 5AZA-DMSO solution using an in-line mixer just before atomization in the spray-drying process. This process limited exposure of the 5AZA to water to just a few seconds, preventing 5AZA degradation during manufacturing. This approach produced SDD powder with good aerosol properties, as well as adequate chemical and physical stability.

Pharmacokinetic Study

A pharmacokinetic study was conducted in rats to evaluate the levels of 5AZA in lung tissue for three administration routes: (1) systemic by intraperitoneal (IP) injection, (2) inhaled aqueous formulation, and (3) inhaled dry-powder SDD (Figure 1).[5] The dry powder was aerosolized using a rotating brush generator and presented to the rats for inhalation through the nose. Both inhaled formulations increased the area under the

FIGURE 1



Pharmacokinetic profiles of 5AZA in lung tissue for dry-powder inhalation, aqueous inhalation, and systemic IP injection. (Adapted from Kuehl et al., 2020).[5]

curve (AUC) in lung tissue 14- to 15-fold compared to the AUC of the systemic formulation that was injected. When normalized for the reduced dose of the inhalation treatments, the AUC was 50-fold higher than that of the systemic formulation. This study demonstrated that local administration to the lung is an effective way to increase 5AZA levels in affected tissue, while avoiding large increases in systemic exposure.

Efficacy Study

An efficacy study was conducted in an orthotopic nude rat model for NSCLC to assess the impact of 5AZA on tumor burden.[5] Briefly, NSCLC cells were instilled intratracheally into the lungs of rats. Twelve cohorts were tested: control (air only), aqueous inhaled 5AZA, and dry-powder inhaled 5AZA were each administered to rats with one of four tumor cell lines. In all four cell lines, the two inhaled formulations reduced tumor burden significantly more than the control (Figure 2). The dry-powder formulation was found to be most effective in three cell lines, and equally effective in the fourth.

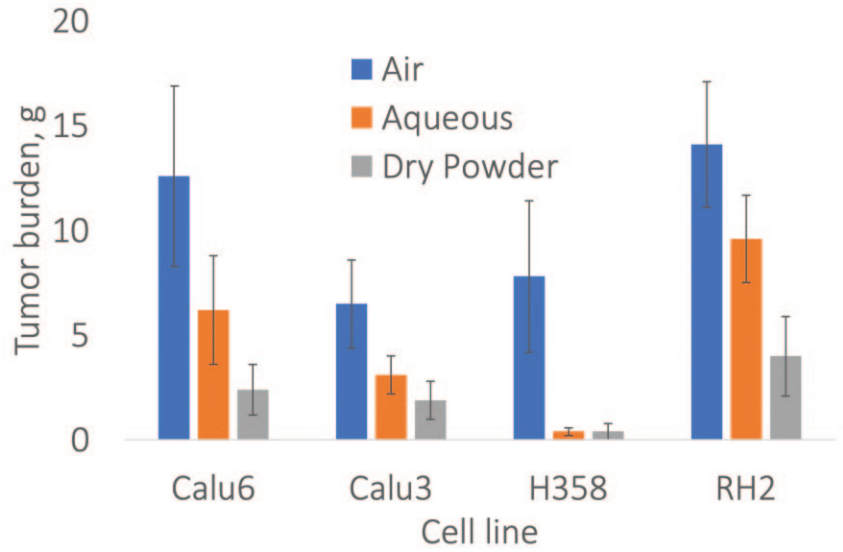
To confirm the mechanism of tumor burden reduction, the number of genes demethylated during treatment was quantified using RNA-sequencing analysis. The dry-powder formulation was found to be superior at transcriptional reprogramming of the genome, compared with the aqueous formulation. The dry-powder formulation delivered high levels of 5AZA to the lung, demethylating the DNA in diseased tissue and thereby reducing tumor burden in the rat model.

CASE STUDY 2: TOPOTECAN

The second case study describes the preparation of a dry-powder topotecan SDD for local inhaled delivery to the lung. Again, the pharmacokinetic performance and efficacy of the SDD was compared to that of an inhaled aqueous formulation and an injected systemic formulation.

The chemotherapeutic agent topotecan is a topoisomerase-I inhibitor used to treat a range of cancers. It was approved for use as an intravenous (IV) infusion in 1996 and as an oral formulation in 2007. Although it is effective at treating lung cancer, its use is complicated by severe hematological toxicity, which can limit dosing in some patients. Topotecan is an excellent

FIGURE 2



Tumor burden of aqueous and dry-powder inhaled 5AZA formulations and a control formulation (air only) for four cancer cell lines in a rat model.

candidate for local delivery to the lung because pulmonary delivery will maximize exposure of lung tissues and minimize systemic exposure to reduce toxicity.

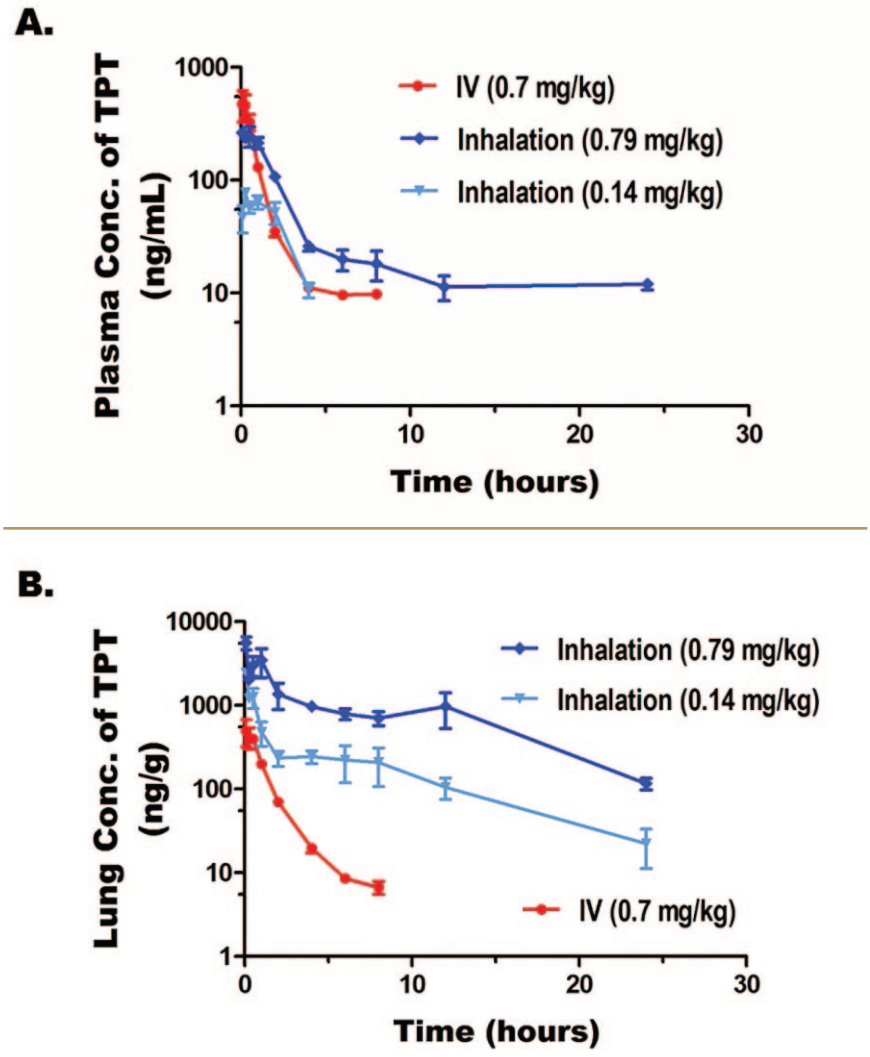
Formulation & *In Vitro* Characterization

Spray drying was used to produce dry-powder topotecan SDD particles that contained 10% topotecan, 70% trehalose, and 20% L-leucine by weight. As topotecan has good solubility in a pH 3.5 aqueous solution, the SDD was manufactured by a standard, single-solvent process. The aerosol properties of the SDD were measured by NGI, showing an MMAD of 2.9 +/– 1.9 microns and a fine particle fraction (FPF) of 62% (% of emitted dose with aerodynamic diameter less than 5 microns). These results indicated a highly respirable dry powder with suitable characteristics for delivery in the deep lung.

Pharmacokinetic Study

A pharmacokinetic study compared lung tissue and plasma levels for two doses of the inhaled dry-powder topotecan SDD formulation (0.79 and 0.4 mg/kg) and systemic (injected) topotecan (at 0.7 mg/kg).[3] Pharmacokinetic curves for lung tissue and plasma are shown in Figure 3. In lung tissue (Figure 3A), the levels of topotecan were much higher for the two inhaled doses than for the injected systemic formulation. The dose-normalized AUC levels in the lung were 895 hr*kg*ng/mL*mg for the injected systemic formulation, and 34,092 and 27,647 hr*kg*ng/mL*mg for the low-dose the high-dose inhaled dry-powder formulation, respectively. Despite the high exposure in the lung tissue, plasma levels remained fairly low for both doses of inhaled topotecan (Figure 3B). The study confirms that a dry powder formulation can be used to deliver high levels of topotecan to the lung while maintaining low systemic exposure.

FIGURES 3A&B



Pharmacokinetic profiles of topotecan in lung tissue (A) and plasma (B) for local inhaled delivery at two doses and IV injection (adapted from Kuehl et al., 2018).[3]

Efficacy Study

An orthotopic nude rat study was designed to compare the efficacy of inhaled and injected topotecan at reducing the burden of tumors grown from two human adenocarcinoma cell lines: (a) H1975, an aggressive and fast-growing cell line, and (b) A549, a moderate-growth cell line.[3] After 25 days of tumor growth, rats were dosed weekly with either 1 mg/kg or 2 mg/kg of an inhaled dry-powder topotecan formulation, 2 mg/kg injected topotecan (systemic), or air only (as a control). Two results from the study are highlighted here. In the H1975 cohort, an aggressive and fast-growing cell line, rats who received the inhaled dry-powder formulation survived substantially longer than those who received the injected systemic or control treatment (Figure 4A). In the moderately-growing A549 tumor cohort, significantly improved tumor burden was observed for the rats who received the in-

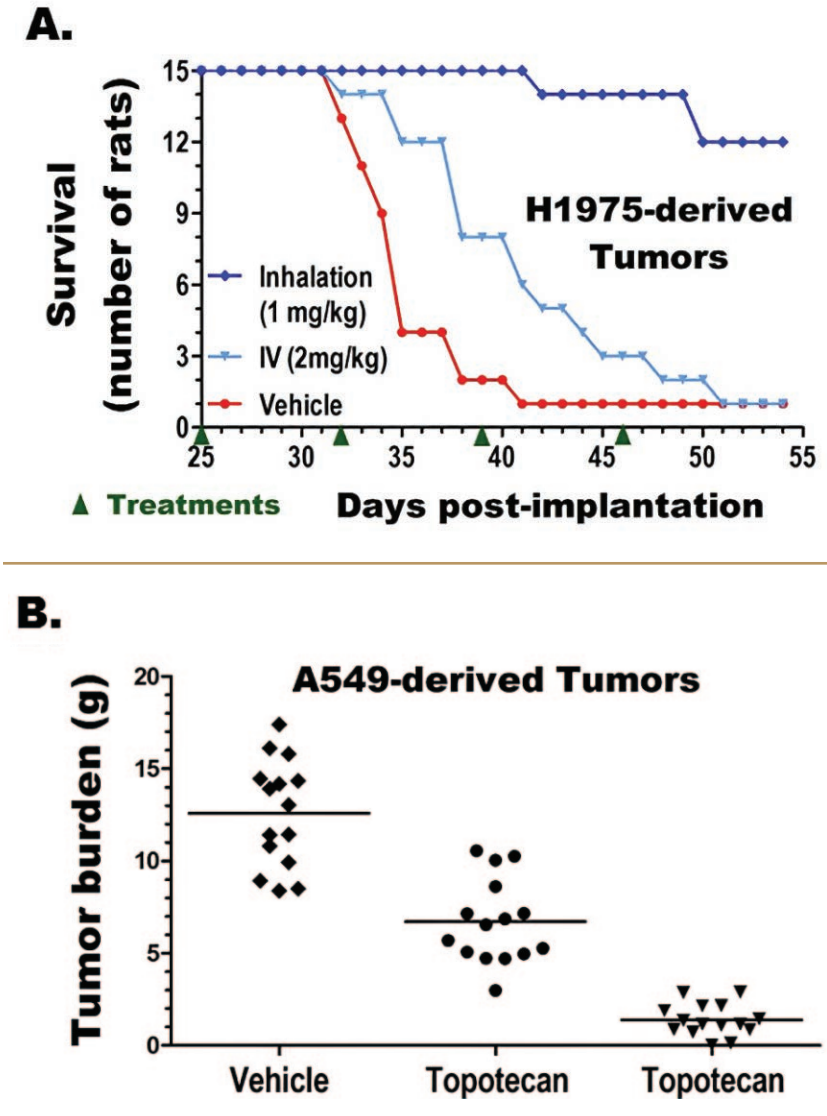
haled dry-powder formulation (Figure 4B). Taken together, these results demonstrate the promising impact of local administration of topotecan for treatment of lung cancer.

OUTLOOK FOR LOCAL TREATMENT OF LUNG CANCER

These case studies demonstrate the potential of local lung cancer treatment to improve efficacy, reduce dose, lessen risk of systemic side effects, and improve patient compliance by providing a convenient dosage form. Specifically, the pharmacokinetic studies demonstrate how greatly improved exposure to lung tissue can be achieved by the inhalation route. Efficacy studies show the impact of this improved exposure on tumor reduction with human lung cancer cell lines. The formulations of 5AZA and topotecan could lead to new options for treating local and metastatic lung cancer, for adjuvant therapy and, when combined with immunotherapy, improve patient survival.

From a manufacturing perspective, spray drying provides a flexible, scalable platform for developing inhaled lung cancer treatments of all varieties. From chemotherapeutics to kinase inhibitors to proteins, spray drying can be used to manufacture stable, respirable, and efficacious formulations for local pulmonary delivery. Multiple inhaled SDDs are currently in clinical trials for a wide range of lung indications, including pulmonary arterial hypertension, idiopathic pulmonary fibrosis, lung infection, and lung cancer. A locally administered treatment holds great promise for improved patient outcomes during primary and maintenance phases of lung cancer treatment. Contract development & manufacturing organizations (CDMOs) with appropriate SDD manufacturing capabilities may help advance these innovative cancer treatments to patients. ◆

FIGURES 4A&B



Survival results for rats implanted with H1975 cells, (A) and tumor burden for rats implanted with A549 cells (B) treated with inhaled dry powder topotecan, IV injected topotecan (systemic), and a control formulation (air only) (adapted from Kuehl et al. 2018).[3]

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BIOGRAPHIES

Dr. Philip Kuehl is a Senior Scientist and Director of Scientific Core Laboratories at Lovelace Biomedical in Albuquerque, NM. He earned his Bachelor's degree in Biochemistry from Hamline University in St. Paul, MN, and his PhD in Pharmaceutical Sciences from The University of Arizona, College of Pharmacy in Tucson Arizona. He is an Adjunct Professor at the University of New Mexico College of Pharmacy.

Dr. Kim Shepard is an Associate Principal Engineer in Research and Development at Lonza in Bend, OR. She earned her Bachelor's and Master's degrees in Chemical Engineering from Stevens Institute of Technology in Hoboken, NJ, and her PhD in Chemical Engineering from Princeton University. Her research interests include pharmaceutical spray drying, amorphous materials, and pulmonary delivery of therapeutics.

PRODUCT DEVELOPMENT STRATEGY

ESCP, Estimating Product Performance Part 3 – Mind the Axle

By: Josef Bossart, PhD

INTRODUCTION

In Parts 1 and 2 of this series, the concept of seesaws, buckets, playgrounds, and leverage were introduced as a model for visualizing the dynamics of pharmaceutical product success. The four key parameters represented as buckets were labeled as **E-Efficacy, S-Safety, C-Convenience and P-Price.** Arranging them on the seesaw and filling them in proportion to their comparative benefit made it possible to estimate the potential success of a new product concept.

THE AXLE

An important contributor to seesaw performance is the axle or pivot and its relative resistance to movement. Walking into a school playground, it is likely the seesaws have not been particularly well maintained, and there is more than a little rust on the hinge, some of which has been removed with regular use. Rust can make it difficult for a seesaw to easily respond to weight differences on either side. In the case of a schoolyard, this is probably a good thing, slowing down responsiveness, if only a little. In the case of pharmaceutical products, friction at the axle can be either useful or not, depending on a company's interests.

THE RUSTY AXLE

Rusty axles in the pharmaceutical sector are generally associated with mature and often low-value indications that see little ongoing development. Few still remain. The commercial incentives to innovate has resulted in these seesaws being tossed out or smoothed with new product introductions, sometimes with the benefit of "lubrication."

A classic example of a rusty axle is the seesaw associated with treatment of angina pectoris with nitroglycerin. The use of nitroglycerin for the treatment of acute anginal attacks goes back to 1878 and its use by William Murrell. The date of the first introduction of a sublingual nitroglycerin tablet is lost in history, but the product was subject to US Drug Efficacy Study Implementation (DESI) regulation, suggesting it was introduced at some point between 1938 and 1962, perhaps earlier. Regardless of when, the use of the sublingual nitroglycerin became a staple of medical practice for the better part of the 20th Century. Its use extended to popular culture with the image of a middle-aged man clutching his chest and reaching for his "heart pill."

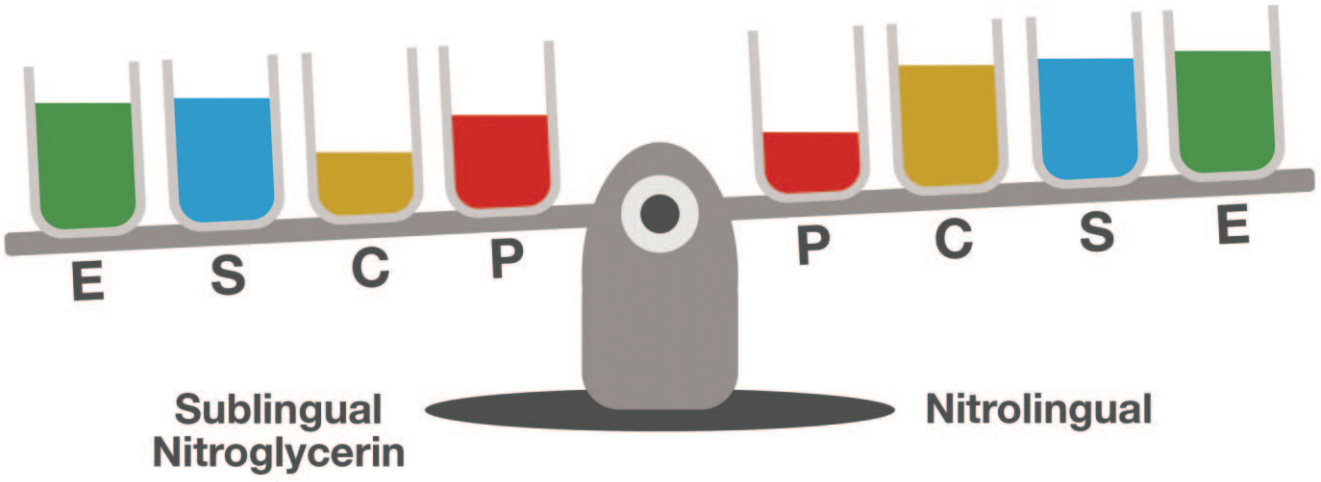
Sublingual nitroglycerin tablets, despite being very efficacious, have suffered from issues of ease of use; dig out the container, take out a single tablet, and then place it under the tongue. Carrying the tablets in a container in a pocket for immediate use, or storing in any type of warmer environment, results in a surprisingly rapid loss of potency. The Efficacy of sublingual nitroglycerin was good, if "fresh." Safety and Pricing were acceptable, but Convenience was not ideal.

That there was an opportunity to improve upon this was recognized by the German-based company Pohl-Boskamp that in 1985 introduced in the US a much more convenient and stable sublingual spray formulation of nitroglycerin, Nitrolingual.

Despite sublingual nitroglycerin being largely unpromoted, Nitrolingual was never able to make much headway in the mar-

FIGURE 1

The Rusted Axle Resists Movement



ket. Being a small new company with relatively limited resources, they ran into a seesaw where the axle was rusted and largely frozen in place.

Physicians who had experience and comfort with sublingual nitroglycerin were not inclined to consider a new product that was arguably better without some sort of a push. The axle of the seesaw was effectively covered in rust. Getting the seesaw to move would take a much greater weight on one side, or some lubrication. Pohl-Boskamp and their licensees never had the necessary resources to properly lubricate the axle or the product "weight" to overcome the resistance. While exact figures are not readily available, it is likely Nitrolingual never reached $20 million in annual sales in the US despite some 5 million annual prescriptions written for sublingual nitroglycerin.

THE GREASED AXLE

Getting an axle to pivot with little friction can be the result of heavy use, the addition of lubricant, or both. A good example of well-greased axles can be found in situations, or seesaws, in which there is generic competition.

Generics by definition are the exact same product as the brand but with a lower price. While there may be examples in which a higher priced product can maintain a significant market share in the consumer drug sector in the face of generics, that is rarely the case with prescription medications. Even a small difference in pricing tips the seesaw to the benefit of the generic.

The prescription market is both well-greased and well-worn when it comes to the entry of generic products. It is almost as though play has shifted to a new seesaw, a high-performance one that is tuned to respond to the even the slightest difference in "weights."

All of this is reflected in the current reality that with the entry of multiple generics, a branded product can lose as much as 90% of its prescription market share within months. The only practical way for branded products to compete is to adjust their price and re-establish a more favorable balance.

GREASING THE AXLE AND SHIFTING BUCKETS

Up to this point, there has seemingly been little accounting for the impact of marketing and promotion in general on the balance of the seesaw. The axle is where promotion has its primary impact, greasing the action and shifting buckets.

Assuming the information provided to the medical community is consistent with a product's approved label, all that promotion can really do is make the market, or in this case a particular seesaw, more sensitive to even slight differences in the bucket weights, individually and in total. A prescriber cannot weigh the benefits of a new product versus what they already use if they don't understand a new product's benefits. Promotion and marketing can help get the message out and frame the benefits of a product in absolute and relative terms.

While considering the market and opportunity for an individual product as competing on a single fixed seesaw is the simplest model; the reality is that each prescriber and formulary will have their own

perception of the fill of each bucket and the relative position of buckets on a seesaw. Moving an Efficacy bucket closer to or further away from the axle will alter the balance of the seesaw. In this way, advertising and a salesperson can tailor a message to physicians and decision makers in line with their preconceived notions, or even help them to rethink their sense of "balance." While the level of each bucket should be consistent between impartial observers based on objective published data, the reality is that perceptions can be "influenced." In time though, the "true" benefits of a product, and how it compares to other products, is revealed with time if there isn't some sort of a "thumb on the scale."

The very best development plan identifies and validates the key benefits of a new product. Attention still needs to be paid to "greasing" the axle so that the benefits in performance can be fully assessed by prescribers and payors. The increasing trend toward independent bodies evaluating the relative value of new products, including Pricing, has made this even more important.

PULLING IT TOGETHER

These are the core concepts necessary to do a "quick and dirty" evaluation of a new product opportunity. How does a product compare head-to-head with a competitor in terms of the four primary characteristics – Efficacy, Safety, Convenience and Pricing? How rusted is the axle? Will it readily respond to the weight of new product benefits, or will it require greasing? In the case of an existing product facing a new and "improved" competitor, the challenge will be to increase friction in the axle and rearrange the buckets to improve comparative performance. Improvement of course is relative, and each prescriber and payor will have an opinion that can be influenced.

Perhaps the benefit of doing a Seesaw analysis early in development is understanding the core parameters and benefits that impact market success. If a new product profile lags in the area of Efficacy or Safety, how can the development plan be adjusted to better demonstrate any benefits the new product might have? Is Pricing the only adjustable parameter? Convenience is an obvious benefit that many companies are exploiting successfully. Both Convenience and Pricing unfortunately offer much less leverage than improvements in Efficacy and Safety.

In the next article, I will review the increasingly common approach of building a new seesaw and sometimes a whole new playground. If you build it, will they come? ◆

Drug Development
EXECUTIVE

Dai Hayward
CEO
Micropore Technologies Inc.

Micropore Technologies

Micropore: Innovation in Drug Delivery

Traditional batch processing is frequently regarded as forgiving of mistakes because they can generally be resolved through post processing. On the other hand, continuous processing has many advantages of stability, repeatability and reproducibility, but is more difficult to establish at the outset because it needs the greater rigour and process understanding epitomised in the principles of Quality by Design. For these reasons, pharma regulators have been driving manufacturers towards the continuous processing. As part of the industry's response to this drive, Micropore Technologies is pioneering the continuous formulation and manufacturing of drug products across a wide variety of administration routes. Headquartered in the biopharma cluster of Teesside, UK, Micropore Technologies serves the pharma and biopharma sectors. Dai Hayward, CEO at Micropore, recently spoke with *Drug Development & Delivery* about the company's expertise and underpinning technology in the development of safe, efficient, and scalable continuous manufacturing of drug delivery solutions.

Q: Micropore's core technology, continuous membrane emulsification, has been around for some years. Why has it only now become of interest?

A: You're correct about membrane emulsification being around for some time – it was identified in Japan in the mid-1980s. Despite its promise of being a gentle process for the manufacture of monodisperse formulations, it struggled to break out of the lab because the technology could not be scaled. That was until 2017 when we launched the Micropore AXF-1, which enabled scale-up to 100 kg/hour. This was followed by the Micropore AXF-7, for use in large-scale applications, which is capable of about 1,000 kg/hour, thereby demonstrating that scaling to a robust manufacturing solution is no longer an issue. We have also harnessed the

"Micropore's relationships are firmly centered on our customers' needs. Many clients come to us for development of their drug product from initial idea to final formulation, while others reach out at a particular point in the development cycle. Our customers rely on a broad range of time-efficient problem-solving expertise and strict confidentiality to protect our relationships. We often start working with a customer as they begin to develop their early ideas about formulation of their drug product. We will develop an optimal formulation for the desired drug delivery route in partnership with our clients."

technology recently to improve the API crystallisation process.

The developments in the technology have resulted in Micropore being awarded several peer-reviewed globally recognized awards over the past few years. In Micropore's hands, membrane emulsification has finally come of age.

Q: What makes Micropore's technology viable as a solution for pharma and biopharma today?

A: Today, Micropore has expertise in all the major administration routes of drug products, especially those that are more complex in nature. We are working with pharma and biopharma in both early stage drug product development as well as clinical trials to enable our customers to bring their products efficiently and economically to market.

Micropore's suite of capabilities runs from early lab formulation development to full GMP capability, starting at a few grams per hour all the way to multiple kilograms per hour.

As a result of our scale-up activities, and somewhat ironically, our pharma and biopharma customers have asked for the scale to be reduced to be able efficiently to cope with GMP operation at the scale in which a few milligrams of product is all that is available for formulation development. We have responded by developing a small version of the AXF-1 to meet this brief while still ensuring scalability for later manufacturing volumes.

We take great pride in being part of the trend toward advanced formulations to enhance large molecule stability or enable new routes of delivery. Colloidal dosage forms, in which Micropore's expertise is increasingly being called upon, like nanoparticles, liposomes and microemulsions, offer many new opportunities for delivery of protein drugs across challenging biological barriers, such as the blood-brain barrier and ocular routes.

Q: I understand Micropore has identified a topically interesting application for its technology?

A: Because of the need for a rapid response to the coronavirus pandemic, the world is in the midst of a paradigm shift in the treatment of diseases through novel developments in vaccine and gene therapies. The overnight success, following decades of development of "synthetic biology" is enabling easily made, precisely programmed, mRNA vaccines to be developed for a number of infectious diseases as well as cancer immunotherapies. The need for a universal modular delivery mechanism has been fulfilled by the development of lipid nanoparticle systems. This plug and play approach of mRNA and lipid nanoparticle will also enable manufacturers to reprogram new versions of approved vaccines in a matter of weeks, allowing almost real-time responses to the emergence of new virus variants.

Our most topical application is our ability to manufacture lipid nanoparticles at the desired size of 80-100 nm at scale. Recently, we've been working with Prof Yvonne Perrie at Strathclyde University to demonstrate the viability of our room-temperature continuous process. We've demonstrated the capacity at over 1 kg/hour and we've not really begun to push the boundaries yet. For both our previous work and this more recent development, we're very confident in being able to achieve 10s if not 100s of kg/hour before the end of 2021.

Needless to say, given the potential for lipid nanoparticles and liposomes unleashed through current coronavirus vaccine programs, we're very excited about contributing to the dawning

of this new age through our "Better Medicines" initiative. We expect to publish the full results from Strathclyde University later this year.

Q: Can you discuss some of the other benefits Micropore's technology offers pharma and biopharma?

A: As I mentioned, our previous work has focused on the manufacture of long-acting, controlled-release microspheres for injectable drug products. One of our licensees, G2GBIO Inc of South Korea, is using the technology to manufacture 1,000 vials per hour of an Alzheimer's therapy, and about 30,000 vials for animal-neutering drugs per hour.

The ability to produce monodisperse materials, of the desired size, means there are no under- or over-sized microspheres to remove in post processing steps such as sieving. This has the effect of ensuring all product manufactured falls within specification and does not produce material that needs to be removed. Micropore has customers that regularly report the need to remove at least 30% of their product. We have many examples of much higher wastage and – because this is generated at almost the final manufacturing step, this material is unrecoverable and is therefore expensive waste. This confers significant operational cost savings as well as offering patient benefits through the use of narrow-gauge needles.

Another notable feature of our technology is its gentle nature. This means we can retain protein integrity at over 90% compared with high-energy processes in which retention is often reduced to about 50%. Clearly, this also brings major economic benefits to the drug manufacturer, in addition to those I've just described, when a smaller dose can be administered that is almost completely therapeutically effective.

Benefits of ease of scale-up using the Micropore approach includes continuous process with very little hold-up, which means small development batches and larger production can be done with the same device.

Q: Micropore works with other companies to innovate drug delivery formulations. How do those relationships work?

A: Micropore's relationships are firmly centered on our customers' needs. Many clients come to us for development of their drug product from initial idea to final formulation, while others reach out at a particular point in the development cycle. Our customers rely on the broad range of time-efficient problem-solving expertise and strict confidentiality to protect our relationships.

We often start working with a customer as they begin to develop their early ideas about formulation of their drug product. In partnership, we will develop an optimal formulation for the desired drug delivery route. Micropore works up to the GMP boundary beyond which, for strategic reasons we do not wish to go, we will work with the customer to ensure a smooth technology transfer to their chosen GMP partner – whether that be in-house or, more usually, to a chosen CDMO.

Q: How many companies around the world are actually using Micropore's technology right now? And how is Micropore structured as a business to provide technical support globally?

A: While still relatively small, Micropore has always been global in outlook. Over 80% of our revenues come from customers outside our home country of the UK. Our customers span the globe from South America to Australasia and are numbered in the hundreds – and this is growing monthly as customers explore for themselves the benefits we bring them. We have invested in establishing subsidiaries in the US and India to ensure a responsive local presence for our customers in these markets. Other subsidiaries are planned. We have also recently appointed a distributor in Japan.

Q: Earlier, you mentioned that you've harnessed your technology for API crystallisation. Would you like to tell us more about this?

A: I have a long personal history in speciality chemical manufacture for API and intermediates. One of the most challenging parts of the process is the ability to produce drug substance crystals of the correct size and morphology. Traditional crystallization processes suffer from uneven mixing, heat transfer, seeding, etc. This results in significant post-processing to achieve the correct size and size distribution – all the while running the risk of degrading the form of the product through high-energy processes, such as jet milling. We have begun building on the conceptual work of our founder, Prof Richard Holdich, at Loughborough University to develop a continuous crystallisation process that delivers the desired size and form of API crystal without the need for downstream

processing, thereby saving both time and money while avoiding the degradation risks inherent in these processes.

We are currently working to expand the range of APIs to include many more. This initiative offers an improved process at the time that many countries have substantial initiatives to return API manufacture to their shores, thereby co-ordinating well with any re-registration process.

Q: I see that Micropore has published a statement about its contribution to the UN Sustainable Development goals. Why have you done this?

A: As a past Chairman of the UK's Responsible Care Board, I have long been committed to our industry being part of the solution to climate change through the development of sustainable business practises. Although we are small, we have the strategic goal of delivering improvements across many of the UN's goals through our customers; whether that be directly, through process improvements, reducing energy use by around 80%, to delivery of zero waste processes or indirectly, through product improvements, such as removal of microbeads from cosmetics to self-healing concrete to lengthen building life. The pharma and biopharma benefits described elsewhere are an integral part of this commitment.

Embedded into our statement is our code of ethics, which was developed by the entire Micropore team and is integral to our approach to all our stakeholders; employees, customers, suppliers, investors, schools, and the local community. It is our goal to "move the dial" in the way we do business to leave the world a better place.

Q: What are the next critical steps for the business to take?

A: As a revenue-generating company with a proven technology and established market position, Micropore is growing rapidly across its chosen market sectors and geographies, but funding is our limiting resource. We are impatient to grow further and faster to bring the demonstrable benefits I've described to the widest possible markets as quickly as possible. For this, we are seeking a corporate investor to join in our growth plans with existing investors. This will allow a rapid reinforcement and expansion of existing capabilities to capitalize on the opportunities in front of us. And, by way of a teaser, we have other ideas about how to deploy the scalable precision of our engineering into new applications. ◆

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POLYVINYL ALCOHOL, UNSPECIFIED **(Tablet/Capsule coat)**	11.72 mg
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FD&C RED NO. 40 **(Tablet/Capsule coat)**	
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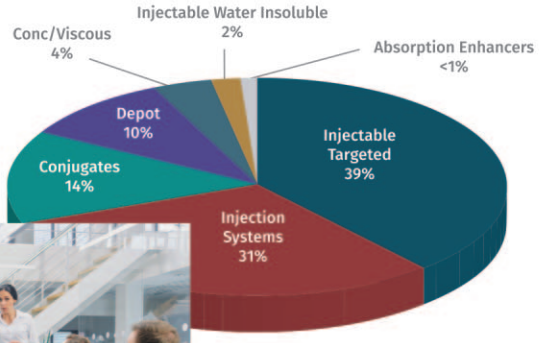

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Special Feature

PFS & Parenteral Manufacturing: How COVID-19 Changed the Market

By: Cindy H. Dubin, Contributor

The global prefilled syringes (PFS) market was valued $4.7 billion in 2019 and projected to reach $10.57 billion by 2026.[1] And innovative and customized PFS are being introduced by market players that want to be key competitors in the global market.

PFS drug delivery is growing in preference over conventional vials because they facilitate benefits such as less risk of overfilling, safe and convenient use, ease of self-administration in a home setting, and lower cost per injection compared to vials or ampoules. "The growth of self-administered injectables is not surprising given the increasing need to reduce healthcare burden via self-administration," says Eric Lee, Director, Business Development at Novocol Pharma. "This has created an opportunity to enhance the use of pens, PFS, and wearable devices. Markets are allowing for more and more injectable-based formulations to be developed for subcutaneous injection by self-administration."

Currently, the majority of PFS are designed to be compatible with biologic drugs. "Year after year, the industry is seeing the increased use of biologics to fight chronic diseases and, in an effort to create better access for patients in

Manufacturing technician inspecting a prefilled syringe at LSNE Contract Manufacturing's aseptic manufacturing facility in León, Spain.

non-clinical settings, the use of prefilled syringes has become the 'gold-standard' for easy and safe self-administration and convenience, particularly with more viscous biological products," says Jeff Clement, Vice President of Business Development, LSNE Contract Manufacturing.

Research on the global PFS drug molecules market shows that among drug classes, vaccines and insulin are expected to be top competitors during the forecast period. However, vaccines lead the market with a projected revenue of over $23 billion by the end of 2027 while insulin will have a higher growth rate.[2] Experts agree this can be attributed to the COVID-19 pandemic.

"The COVID pandemic has accelerated the move to patient self-treatment and remote physician consultations," says George I'ons, Head of Product Strategy & Insights at Owen Mumford Pharmaceutical Services. "Many patients are now more willing to treat themselves and manage their conditions with less face-to-face interaction with healthcare professionals. This set of circumstances has helped to drive the growth in autoinjectors and prefilled syringes as a method to self-administer medication."

Wearable Injectors & Connectivity

Large-volume wearable for subcutaneous self delivery have become a preferred choice for administration of drugs in the homecare setting. Variants of these wearable devices have been designed to administer highly viscous drugs (such as biologics) in large volumes (more than 1mL), offering numerous dosing options (basal, bolus or continuous), integrated safety mechanisms, and an almost negligible risk of needlestick injuries. According to recent research, the field is witnessing innovation with the development of integrated mobile applications with smart health monitoring, artificial intelligence – including provisions for reminders, the ability to connect to web-based portals for sharing medical data with the concerned healthcare providers, visual/audible drug delivery confirmation notifications, automatic drug reconstitution, and error alerts. The researchers believe that such efforts will drive growth this market over the coming years.[3]

"The increase in remote patient treatment has driven the need for more drug delivery devices to offer the option of connectivity," says Mr. I'ons. "In addition, the desire to improve therapy adherence and, in turn, hopefully improve patient outcomes is positively influencing this trend. Connected autoinjectors allow the simple transfer of key patient data on treatment time and dose delivery confirmation as well as the option to collect additional data. Connected devices now provide the means to create a 'dialogue' with the patient and provide training, education, and disease management information, and tools via apps. In the future, this technology will provide a variety of ways to increase engagement with patients as well as being able to identify issues with treatment regimens and provide the necessary corrective actions."

Environmental & Cost Concerns

Despite myriad benefits, there are environmental and disposability concerns over single-use autoinjectors and PFS. This is increasing the need for products with sustainable features, environmentally friendly materials, and leaner and cleaner manufacturing processes and supply chains. Another hindrance in the growth of the PFS drug molecules market is being attributed to the premium pricing of autoinjectors. This is being linked to the complex development process.

This annual *Drug Development & Delivery* report explores how device developers and parenteral contract development and manufacturing organizations (CDMOs) are addressing these challenges, as well as advancements in customized device design, the continuous effort to incorporate safety and human factors, and how COVID-19 is shaping the future of the market.

AJINOMOTO BIO-PHARMA SERVICES: Expanding Aseptic Fill/Finish Capacity

Increased demand for outsourcing parenteral CDMOs is being driven by the increasing number of emerging biopharma developing their own products through late stage. Additional demand is coming from the increase in targeted, potent, and orphan drugs as well as the continued growth of biologics.

Ajinomoto Bio-Pharma Services offers complete parenteral manufacturing services on three automated vial fill lines and one automated pre-

Aji Bio-Pharma offers a range of formulation and aseptic filling in prefilled syringes for clinical and commercial products.

filled syringe fill line. In addition, the CDMO has an automated fill line, housing an inline lyophilizer, dedicated to highly potent products. Filling capacity with high speed is being expanded to include a high-speed, multipurpose fill line, which will be fully operational this summer.

"This expansion provides a 50% increase in our current aseptic fill/finish capacity and allows for additional scheduling flexibility, as well as component flexibility," says Reggie Branch, Manager, Drug Product Manufacturing, Ajinomoto Bio-Pharma Services. "The new fill line offers a range of configurations, including prefilled syringes, cartridges, and vials; utilizes isolator barrier technology to ensure the required sterility for fill finish; and uses ready-to-use components, which minimize component preparation and packaging."

The increased need for CDMO services is also coming from the current focus on COVID-19 projects. In 2020, Ajinomoto Bio-Pharma Services partnered with a client that needed several lots to be produced to support ongoing COVID-19 efforts, and wanted to achieve delivery in the most efficient time possible. "They signed their first contract in April, and we were able to fill their first run by June," says Mr. Branch. "There were several stakeholders that came together and worked very hard to meet this aggressive timeline without sacrificing quality. Ultimately, we produced approximately 45,000 vials for the client to be used during clinical trials with their patients."

AMRI: Is 2021 the Year of the PFS Revolution?

Over the last year, all eyes have been on COVID-19. But the scientific community's success in developing multiple, life-saving vaccines has had a ripple effect across the drug manufacturing pathway. These vaccines are now being produced by the millions, which has resulted in a vial manufacturing capacity shortage that is affecting other important areas of medicine. Fortunately, there is a solution that just so happens to come with ample positive side effects: prefilled syringes.

The advantages of PFS over traditional needle and vial delivery systems have been well-documented. PFS are easy to use and ensure accurate dosing. This makes them ideal for people with long-term conditions who must regularly self-administer medicines, such as monoclonal antibodies. Additionally, PFS reduce needlestick injuries and, because they deliver precise dosing, slash waste and the likelihood of potentially dangerous dosing errors, says Anish Parikh, Vice President, Drug Product Sales & Marketing, AMRI.

Further, Mr. Parikh says PFS are better suited than traditional vials for use in emergency situations and remote areas, enabling medicines and vaccines to be delivered, for example, by aid workers or support workers, with less medical expertise.

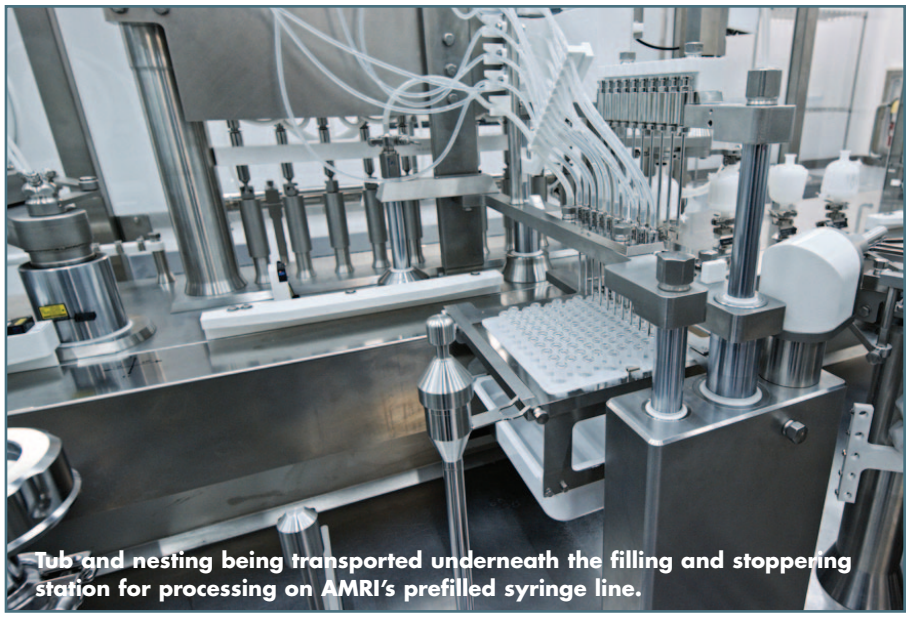
"Thanks to advances in filling technologies, PFS is now suitable for even more medication types than it was before, such as small-molecule drugs," he says. "This leads some to believe that COVID-19 vaccines, currently being delivered via needle and vial, could soon make the shift to PFS. Any doses currently left in the vial after use are wasted, and as the vaccine roll out gains pace in low- to middle-income countries, healthcare systems will be looking to utilize non-medical staff to deliver doses. This means PFS has the potential to help manufacturers overcome the vial shortage, while enhancing safety and patient experience."

Well-established PFS experts have the knowledge and the technology to work with partners to design processes for all types of medications. They have the technology – rotary piston, peri-

staltic, or rolling diaphragm pumps – to meet the needs of even the most viscous or complex suspended product.

And, due to COVID-19, PFS experts have renewed focus on efficiency. AMRI, for example, has worked with pharmaceutical partners to slash lead times, in some cases from 15-18 months to less than 10. And, Mr. Parikh says AMRI also offers greater efficiencies via a full end-to-end service, from API processing to fill/finish.

"Those of us in the sector have known that PFS is the future for some time," he says. "Over the last year, the wider industry, while driven by necessity, has also started to understand the added benefits this mode of delivery can offer when compared to traditional needle and vial systems."



Tub and nesting being transported underneath the filling and stoppering station for processing on AMRI's prefilled syringe line.

APIJECT SYSTEMS CORP.: New PFS Made Via Blow-Fill-Seal

Worldwide, the parenteral market is seeing greater emphasis on patient safety. This is driving a strong trend toward unit-dose formats, including prefilled syringes, which are now the fastest-growing format for injectables.

"A prefilled syringe eliminates the middleman, significantly reducing pharmacy staff workloads because there is no need to fill all those individual syringes," says Beth Totin, Chief Commercial Officer at ApiJect Systems Corp. "Automated prefilling lessens the likelihood of medical dosing errors, reducing patient harm and reducing potential caregiver liability."

ApiJect has developed a new prefilled injector that delivers these benefits while realizing significant economies of scale through Blow-Fill-Seal (BFS) manufacturing technology, explains Ms. Totin. "A single BFS production line can manufacture up to an estimated 25,000 of our unit-dose PFS devices per hour, potentially at a cost per dose delivered that is comparable to, or below that of, a multi-dose vial and associated disposable syringes."

She notes that the ApiJect prefilled injector has been submitted for review, but has not yet been approved by FDA or other regulatory authorities.

Demand for primary packing of COVID vaccines has caused a significant number of fill/finish lines to reduce or halt production of regular vaccines to free up emergency capacity for COVID vaccines. ApiJect is addressing this challenge with a compact supply chain and high-speed, high-volume manufacturing. "Only pharmaceutical-grade resin and stainless steel are needed to make our prefilled injectors," she says. "Both raw materials can be domestically sourced and stockpiled, reducing the risk of international supply disruptions."

The future ApiJect Campus in Research Triangle Park, North Carolina, has been designed to deliver production capacity of 2 to 3 billion units annually with 15-plus BFS lines, each in a BSL-2 environment suitable for vaccines and a range of other injectable drugs. The first BFS line is expected to commence operations by late 2022.

APTAR PHARMA: Vaccine Platform Addresses COVID-19 Developments & Life Cycle Management

The academic research, pharmaceutical, and medical technology industries have come together to develop, test, produce, and deliver COVID-19 therapies and vaccines. Aptar Pharma has been at the forefront of this response.

To date, 13 vaccines have received approval and many more are currently under development and trial. Regulatory approval is obtained not only for drug formulation but also for the primary container with which the drug is in direct contact. Therefore, choosing the right container and clo-

Aptar Pharma Vaccine Platform includes: PremiumCoat® ETFE film-coating syringe plungers and vial stoppers, rigid needle shields, tip caps, and vial stoppers for liquid and lyophilization applications.

sure solution is essential to mitigate the risk in the development stage, obtain rapid approval to release the drug on the market, and secure the supply for large-scale delivery.

As vaccination campaigns are rolled out, the emergence of new COVID-19 variants suggests that, once under control, this pandemic could become a seasonal epidemic, says Audrey Chardonnet, Business Development Director, Aptar Pharma. "Drawing from our experience with the flu, we know seasonal vaccination is very different from the mass vaccination context we are currently experiencing. Instead of relying on large vaccination centers, where many vaccinations are performed sequentially, seasonal vaccines are usually administered by trained nurses, physicians or even pharmacists directly in their offices. In this context, single-dose prefilled syringes become highly relevant, as they limit drug waste compared to multidose vials and dramatically simplify the administration process. Preparing now for the transition from vials to prefilled delivery solutions is essential."

Aptar Pharma's vaccine platform approach, which includes complete PFS closure solutions, rigid needle shield solutions for staked needles, and various tip-cap designs for luer applications, is designed to de-risk and accelerate pharma partners' vaccine developments. Ms. Chardonnet explains that COVID-19 vaccine manufacturers are selecting Aptar's PremiumCoat® stopper with state-of-the-art ETFE film coating technology to reduce risks linked to extractable and leachables, as well as for its performance in multi-piercing situations. "Our vaccine platform can support our pharma partners by delivering complete PFS closure solutions," she says.

AUGUST BIOSERVICES: Full-Service CDMOs Will Meet Growing Industry Demands

Prefilled syringes and parenteral contract manufacturing reside at a fascinating crossroads in 2021," says Joe Mase, Executive Vice President of Operations for August Bioservices, a full-service, US-based, and injectables-focused CDMO. "In many ways, there has never been more momentum, strategic intent, and innovative product development behind ready-to-use, easy-to-administer drugs like prefilled syringes," he says. "When you consider the benefits of patient safety, uniform dosing, and caregiver and patient convenience, prefilled syringes are understandably preferred mechanisms for drug delivery today. Yet, at the same time, these opportunities also are running into headwinds that could potentially stunt their production plans, launch schedules, and market adoption."

Of course, COVID-19 has had a significant impact on the global contract manufacturing industry. Supply chains have been strained to the breaking point. Vetting of new potential vendors via on-site audits was restricted. The sourcing and delivery of critically needed materials, from API to components, have proven difficult, causing project timelines to shift beyond scheduled milestones and deadlines. Further exacerbating the problem is the dearth of available manufacturing capacity for prefilled syringes and parenteral manufacturing – especially in the United States. Moreover, a large portion of production slots that, under normal circumstances (in a non-COVID world),

would have gone to a wide range of PFS products, have been allocated to producing vaccine.

Mr. Mase further explains the downstream impact. "While experts say a rise in chronic diseases is driving the injectables market, less widely understood and appreciated is the limited number of CDMOs with the requisite expertise and experience in injectable aseptic manufacturing to service this increasing demand efficiently and effectively. Fewer still have the equipment, capacity, and cGMP experience to successfully handle drug formulation development, clinical and commercial manufacturing, extractable and leachable testing, stability testing, terminal sterilization, as well as products that require lyophilization."

BD: Recognizing Trends in Volume, Dosing, Storage, Traceability & Production

As biologics are increasingly being considered for home self-administration, key design space parameters are evolving to encompass 2mL volumes (and more) with viscosities up to 30cP and beyond. These new formulations present design challenges, such as a potential increase in total injection time, patient discomfort, and issues with mechanical injection force. The BD Intevia™ 2.25mL disposable autoinjector platform combines a handheld autoinjector and a prefillable syringe in one integrated system, specifically designed for high-viscosity and/or higher-volume biologics. The integration of the BD Neopak™ XtraFlow™ 2.25mL glass prefillable syringe, featuring an 8mm extra-thin wall needle, supports injection of higher drug volumes and viscosities, and combination product performance. "With this solution, BD aims to enhance comfort, safety, and convenience for patients," says Marie-Liesse Le Corfec, Global Portfolio Marketing Head, BD Pharmaceutical Systems.

Larger doses and higher viscosities are also trending as pharmaceutical companies respond to the move from intravenous to subcutaneous routes of administration, and from acute to non-acute care settings. Ms. Le Corfec says that multiple comparative studies show that patients and healthcare providers prefer subcutaneous to intravenous administration, citing improved clinical management, efficiency, and convenience with decreased pain and adverse effects. In response, the BD Libertas™ wearable injector has been developed to enable subcutaneous self- or care-giver administration of 2-10mL and up to 50cP viscosity. She says BD has conducted more than 50 preclinical and clinical studies to inform system design, measure performance, demonstrate the feasibility of 2-10mL subcutaneous injections, and characterize tissue response. The most recent clinical study with the investigational wearable injector demonstrated functional performance with broad acceptability across subject genders, body mass index categories, and age range, with and without movement.

Production capacity is a factor that could potentially restrain the injectables market. Recognizing this, BD is investing approximately $1.2 billion over a 4-year period to expand and upgrade manufacturing capacity and technology for prefillable syringes and advanced drug delivery systems across its 6 global manufacturing locations. A new manufacturing facility

August Bioservices formulates, manufactures, and tests drug products in aseptic or terminally sterilized vials, PFS or cartridges, and fill IV bags from 25mL up to 5 liters.

in Europe is also included in the investment package. "The investment will also fund new product innovations, manufacturing technology enhancements, and business continuity improvements, all designed to maximize supply and reduce risks for pharmaceutical companies that rely on ready-to-fill injection systems for their drugs — including biologics, vaccines, and small molecules," Ms. Le Corfec says.

The BD Traceability program is a new dimension to the BD offer. BD will supply syringes identified with serial numbers, the hardware to read the serial numbers on pharma manufacturing lines, and the workflow/analytics software to process the data. She explains that the benefits for pharma customers of unit-level identification and automated container identification can include control of container integrity throughout the value chain and digital access to each container's production data, intended to prevent product mix-ups prior to labelling, to automate batch segregation and reconciliation, speed up investigations, and limit the number of batches affected by a quality issue. The BD Traceability solution is meant to have no impact on customers' existing production line speed.

A number of COVID-19 vaccines require frozen storage during deployment. BD is building on its experience with BD Accuspray™ Nasal Spray System for -25°C storage, as the company evaluates the performance of its PFS containers under deep cold storage conditions during the development and ongoing lifecycle management of the PFS containers.

BIOPHARMA SOLUTIONS: Developing & Testing PFS Formulations

Advancements continue in the development and use of prefilled syringes. For example, an aging population and the increase of diabetes create a need for intravitreal injections. And aging patients diagnosed with macular degeneration and diabetic patients with decreased blood flow to the eye may find benefit in low-dose PFS to deliver biologics and steroids to the back of the eye.

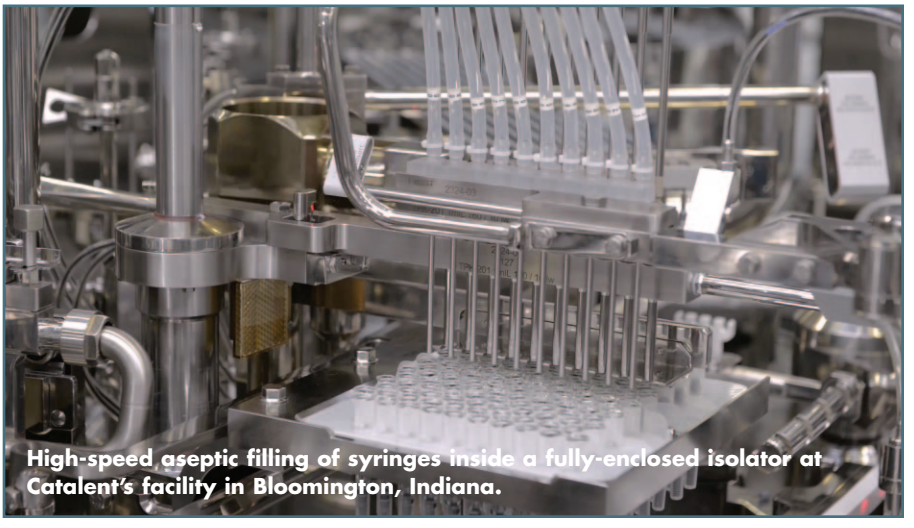
Recent advancements in PFS provide more options for the market. This includes polymeric syringes that do not require application of silicone to the barrel of the syringe to allow easy movement of the plunger. Another is a hybrid syringe that is mostly polymeric with a fine application of a glass layer that decreases the water vapor transmission rate and the exchange of oxygen through the polymer. The syringe contains a plasma deposition layer of silicone that provides no free-silicone that could interact with the product or be deposited in the eye.

"BioPharma Solutions (BPS) is well experienced with developing and testing formulations in PFS, converting from a vial to PFS, as well as in understanding the details required for transferring ready-to-use syringes to the grade-A area," says Gregory A. Sacha, PhD, Senior Research Scientist at BPS, a unit of Baxter. Controlling fill volumes and decreasing the variability in plunger placement are other services that BPS can service clients, he adds.

"The experience of our Bloomington, Indiana facility helped aid in producing prefilled syringes containing diluents such as sterile water for injection and sterile 0.9% saline for injection," he explains. "The diluent injections are available in a range of volumes and can be paired with a product in a vial to ensure the exact volume of diluent is added."

CATALENT BIOLOGICS: Methodology Improves Process Design

PFS composition and design have been improved in the last year. Examples include: a low-tungsten forming process for glass syringes that helps avoid interactions with the biologic drug product and increases a product's shelf-life; specific thin-walled



High-speed aseptic filling of syringes inside a fully-enclosed isolator at Catalent's facility in Bloomington, Indiana.

needles that enable the injection of highly viscous biopharmaceuticals; and improvement of dose accuracy through a better management of syringe tolerances. Additionally, some autoinjectors have become e-Devices, with reusable electronic injection parts, and a design focused on patient ergonomics and safety.

Catalent Biologics provides comprehensive global solutions from development and biomanufacturing to fill/finish of vials and syringes, device assembly, and packaging for pharmaceutical companies' biologics and sterile injectables, beginning as early as the pre-clinical stage through commercial launch.

According to Natasha Van Rutten, Director, Product Development, Catalent Biologics, customers are coming to Catalent with different levels of cGMP and scale-up needed for the commercialization of a biologic or sterile product. "In order to ensure that products are developed or transferred in the appropriate method and timeframe, Catalent has created a complete methodology, ensuring that all critical data are either captured or generated in the early stages of the project," she explains. "The data are managed so that the resulting manufacturing processes are appropriate, developed within the required timeline, and with the lowest level of risk."

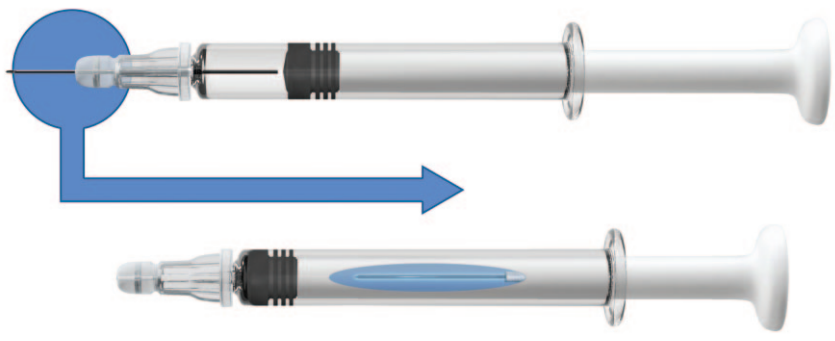
The methodology starts with a gap analysis, allowing the identification of what data are missing and needed to start the process design stage at the beginning of development or tech transfer. Using this methodology, Catalent supported a customer developing a PFS product that had severe clogging issues during drug product (DP) filtration prior to the filling step with its previous manufacturing partner. Through an appropriate gap analysis, it was demonstrated that certain critical information was missing for the DP. A Design of Experiment (DoE) was proposed and performed showing that a process parameter was not set appropriately, causing the clogging during filtration. Catalent's scientific expertise solved the DP filtration problem and supported the successful commercial launch of the pharmaceutical drug.

CREDENCE MEDSYSTEMS: Meeting Diverse Market Needs

Two important factors influencing the injectable medication market are the continuing rise in the prevalence of chronic disease patients as well as the significant increase in vaccination requirements stemming from COVID-19. While the impact of each of these factors is significant, they represent different use cases and some different requirements.

The chronic care market is often characterized by injections occurring out of the formal healthcare setting by patients and their caregivers. A premium is placed on ease of use and user cues to help guide proper injections, and the market includes users who prefer an autoinjector as well as those who prefer the 'direct injection' from a syringe. On the vaccine side, injections are performed by healthcare providers, needlestick safety and reuse prevention are critical, and total cost of ownership constraints are often more stringent. Both markets share the need for minimizing the environmental footprint, maximizing a platform approach that yields consistency across both ready-to-inject formulations and those requiring reconstitution at the point of delivery, and compatibility with industry-accepted syringe barrels and closure components.

Credence MedSystems invented and developed its Companion® and Dual Chamber Reconstitution Syringe™ product lines to be flexible enough to meet the diverse needs of these markets, says John A. Merhige, Chief Commercial Officer, Credence MedSystems. Both products integrate with standard syringe barrels and use industry-standard closure components. "The Companion allows pharmaceutical manufacturers to provide critical usability and safety features to



The Credence Companion® and Dual Chamber Reconstitution Syringe™ meet the needs of the vaccine and chronic disease markets.

their end-users," he says. At the completion of the injection, the user receives end-of-dose cues indicating that the full dose has been delivered, and the needle automatically retracts into the syringe barrel preventing reuse. "The Dual Chamber Syringe introduces the additional benefit of single-step mixing and injection, or the sequential injection of two liquids. Both products offer broad flexibility, a consistent user experience across the platform, a minimized environmental footprint, and potential compatibility with autoinjectors."

Credence recently announced a strategic investment from Novartis intended to advance ongoing development and scaling of Credence's drug delivery systems. Assisted by this investment, which confirms Novartis' interest in employing Credence technology for its injectable medicines, Credence has initiated scaling of its manufacturing capability to meet customer demand. The production capability will include both the Companion and Dual Chamber products. An additional collaboration between Credence and SCHOTT for the application of Credence technology with SCHOTT's prefillable glass and polymer syringes is directed at further ensuring readiness of the supply chain, he explains. "With multiple enabling strategic collaborations in place, Credence is poised to bring its innovative technology to the market to meet the complex needs of the vaccine and chronic disease use cases."

DUOJECT MEDICAL SYSTEMS: Off-The-Shelf Solutions Are Becoming Impractical

There is increasing interest for devices with performances tailored to specific formulation needs (i.e., fill volumes, injection volumes, injection time, needle requirements, container materials, etc.). This need is driven, in part, by the prolific development of complex drugs like biologics, the rise of home care treatments, and increasingly stringent regulations, says William Fortina, Business Development Director, Duoject Medical Systems. In response, device developers are focusing on simple-to-customize platforms; off-the-shelf devices or legacy systems (vials and syringes) are no longer appropriate, he says.

"Medical devices for parenteral administration must be capable of dealing with subcutaneous injections, viscous formulations, large injected volumes, controlled injection speeds, and thin needle gauges."

In recent decades, pharmaceutical companies have been able to commercialize many small molecules, including generics, using off-the-shelf delivery systems. But, Mr. Fortina says increasingly specific treatments and complex molecules demand a customized approach to drug delivery system development, making off-the-shelf solutions less practical. "Approaching such projects requires a different mindset, which proved difficult for many players in the market," he explains. "For instance, life-saving rescue autoinjectors in the US market must now be proven to be reliable 99.999% of the time with 95% confidence. The only way to achieve this is to collaborate closely with the device developer and manufacturers, as no off-the-shelf delivery system can achieve this without being developed and extensively tested hand-in-hand with the intended drug."

When it comes to treatments for chronic diseases, injection requirements are becoming more drug- and patient-specific (i.e., less flexible formulations). Moreover, a growing amount of such treatments are aimed towards home care and self-administration. "Most off-the-shelf drug delivery systems cannot meet the injection and usability requirements of such treatments," says Mr. Fortina. "For these reasons, medical device development or platform customization is often the only viable way. This is, and will remain, an important challenge to the commercialization of new treatments."

The challenges described above lead many pharma companies to contact Duoject Medical Systems to develop devices for drug reconstitution and administration. Duoject has a large portfolio of patented platforms that can be customized to specific needs, but also offers end-to-end medical device development services. "There are many advantages to offering a medical device tailored for a specific treatment because it often results in fewer risks and a stronger presence on the market," he says.

Flex Health Solutions created the prototype of a low-cost, smart, prefilled syringe module for its pharma partners to improve adherence.

FLEX HEALTH SOLUTIONS: Electronics & Human Factors Are Equally Important

The proliferation of connectivity and app-based tracking of usage, dosage, and adherence is an important advancement in the PFS market. An exemplary smart syringe solution integrates a small electronic module, which transfers key information to a cloud-based system for further analytics.

Just as critical is the integration of sophisticated sensors to support proper positioning and use, which is helping to usher in the era of highly user-centric designs. The fast-growing, home-based healthcare market will require such patient-friendly designs.

In fact, human factors are equally important to ensure ease of use. "We have worked with customers to consider the full patient journey and perspective: from the first step where the syringe is taken from the package and paired with a smartphone, to its handling at injection time, and finally to its environmentally friendly disposal," says Marco De Angeli, Senior Director of Design, Flex Health Solutions. As a design-led CMO, Flex leverages and integrates core and emerging technologies, such as connectivity/Internet of Medical Things (IOMT), sensors/actuators, and printed batteries to optimize value in a range of medical products, including wearable injectors. Biologics that are traditionally delivered intravenously may be able to be delivered in a wearable pump applied by the patient. And personalized medicine, which makes the therapy more specific to the patient, may increase the need for various wearable pumps or other injectors that can be user filled, he says. Increased patient responsibility means that designs must be intuitive and easy to use. Here, again, human factors engineering built into the design is desirable and necessary.

Another trend is digitization of user interactions, where drug injection and environmental data are collected via sensors from the drug injection. The data is transferred to a backend medical mobile app/Cloud. "This allows the generation of customized therapies and direct interaction between doctor and patient," says Mr. De Angeli. "Flex is working with customers to develop solutions for connected prefilled syringes that incorporate the latest interoperable low-power technologies (NFC-BLE) and is supporting customers in designing and developing machine-learning engines hosted as web services in a medical cloud engine."

With connectivity comes concern about cybersecurity and the remote connection between medical devices and backend application. Flex helps customers mitigate cybersecurity risks by incorporating security into the device design, the mobile application, and the manufacturing infrastructure for smart prefilled syringe devices.

Because a prefilled syringe is disposable, cost must be factored into the system without compromising on quality and reliability, he stresses. "For cost effectiveness and a minimized footprint, the electronics should be fully integrated into a single silicon chip and have the right sensing and communication architecture. In demonstrating a proof of concept, Flex has created the prototype for a compact, low-cost add-on module, utilizing specialized engineering competences, such as radio frequency design, to optimize the antenna footprint, and sensor processing to achieve a reliable end-of-dose event."

LSNE CONTRACT MANUFACTURING: Reliable & Flexible Aseptic Filling

LSNE brings an integrated approach to pharmaceutical manufacturing of parenteral drug products. LSNE added PFS capabilities to its

portfolio in 2019, and can support syringe sizes from 1-3mL with fill volumes as low as 0.1mL.

"We are seeing the market trend towards the increased use of prefilled syringes and anticipate continued market growth as the PFS presentation provides a host of benefits by limiting the waste of valuable drug product, allowing for precise administration, is user friendly and convenient for acute care or emergency use, improving safety, and are amenable to many autoinjector formats," says Jeff Clement, Vice President of Business Development, LSNE Contract Manufacturing.

As the parenteral market continues toward an outsourced model, LSNE has made it a mission to provide consistency from formulation through aseptic filling. Its manufacturing suites are built with reliability and flexibility in operations, especially for complex formulations and high-value products that require minimal product loss. "LSNE meets all these challenges with a prefilled syringe line approved for both clinical and commercial products," he says.

LSNE has experience with a range of drug product classes, including mRNAs, monoclonal antibodies, oligonucleotides, and challenging small-molecule therapeutics, as well as formulation methodologies such as liposomal formulations, non-aqueous formulations, suspensions, and emulsions.

MITSUBISHI GAS CHEMICAL COMPANY, INC.: Plastic Vials Will Be Popular This Year

"There is a shortage of glass containers because they have been used for COVID-19 vaccines so we expect the use of plastic containers will be more popular in 2021," says Tomohiro Suzuki, Associate General Manager Business Development Department Advanced Business Development Division, Mitsubishi Gas Chemical (MGC) Company, Inc.

MGC supplies plastic containers, which have high water vapor barrier, very low extractables, low protein adsorption, high break resistance, and excellent pH stability, he says.

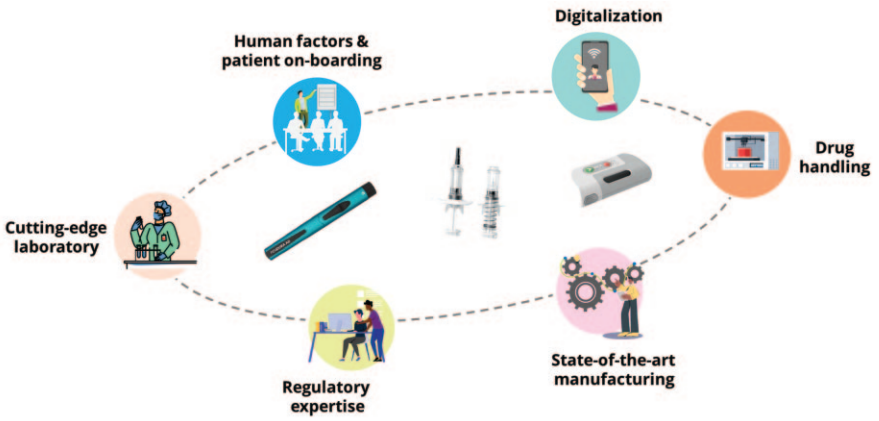
Mr. Suzuki says that there is increasing interest in ready-to-use plastic vials that feature cold storage resistance. "This is especially beneficial as biologics and drugs for gene and cell therapies are often stored at ultra-cold temperatures.

MGC's OXYCAPT™ plastic vials are suited for parenteral pharmaceutical liquid medication storage. OXYCAPT's multilayer construction preserves drug stability and shelf life in plastic vials, with significantly reduced oxidation, compared to cyclo olefin polymer (COP). Long-term trials find OXYCAPT eliminates the problem of delamination (visible small flakes and particles from glass deterioration over time) in glass, while maintaining its oxygen barrier. OXYCAPT also resolves poor stability and low visibility issues found in plastics, he says.

NEMERA: Range of Devices Ease Self Administration

A rising number of pipelines in biologics and biosimilars require adequate drug delivery device solutions to accommodate sensitive drugs for safe self-administration. This has been exacerbated in the wake of the COVID-19 pandemic as patients are reluctant to visit hospitals to receive their therapies. Moreover, the switch from intravenous to subcutaneous drug administration in a home care therapy setting is emerging, driving the need for sustainable solutions. To cater to these needs, the pandemic drove digital health and sustainable solutions to come to light. With the converging

OXYCAPT™ multilayer plastic vials and syringes from Mitsubishi Gas Chemical.



Nemera's comprehensive portfolio of parenteral delivery systems and integrated services.

trends of digitalization, electronics are being actively developed to be integrated within the drug delivery devices.

Nemera has bolstered its portfolio to address these trends and offers a range of parenteral delivery systems. Safe'n'Sound® is a highly customizable, passive safety device available in 1mL and 2.25mL formats, suitable for both skilled and novice users. An overcap, rigid needle shield (RNS) puller assists patients with dexterity issues, explains Severine Duband, Category Director, Devices, Nemera.

A range of Nemera pen injector platforms treat various pathologies thanks to the recent acquisition of Copernicus. A spring-assisted pen injector, coupled with a side-actuator button, enables users to stabilize the hand by resting it against the body during administration for seamless injection. "We understand the ergonomics for patient compliance and adherence to therapies is crucial," she says.

Finally, a patient-focused on-body injector platform is designed for seamless and user-intuitive delivery of large volumes (20mL), with reusable and disposable parts for sustainability and cost efficiency.

"Through capabilities in human factors engineering, design research, user experience design, lab services, and regulatory support, Nemera can support customers with an integrated device platform and service program," says Audrey Chandra, Category Project Manager for Nemera.

NOVOCOL PHARMA: Turnkey CDMO Supports Integrated Multi-Party Activities

Novocol Pharma specializes in sterile cartridge manufacturing. Over the past 5 years, and most recently, Eric Lee, Director, Business Development, has witnessed an incremental demand for cartridge-based injectables for self-administration. In fact, within the total injectable market, self-administered injectables consisting of cartridges-based pen injectors and PFS showed the largest growth.

As a sterile cartridge-focused CDMO, Novocol plays a key role in supporting the development and commercialization of the growing self-injection market. Its focus is on providing full turnkey services from product development support and tech transfer to fill/finish and final device assembly. "With our expertise and understanding of combination products, we assemble standard pen injectors using flexible in-house, pilot-scale assembly equipment and are also accustomed to running customized customer-dedicated assets," says Mr. Lee. "With both GMP and ISO 13485 certifications, we are capable of providing a turnkey offering meeting the quality rigors for both drug products and medical devices. In addition, we have the necessary infrastructure to handle challenging product types including highly-potent APIs, controlled substances, and temperature-sensitive products."

Given the additional complexities associated with both sterile injectable manufacturing and integration with a device for self-administration, it is highly challenging for pharma sponsors to manage and coordinate multi-party activities between the drug developer, CDMO, and device developer. Working with a CDMO and medical device developer who have previous project experience together can significantly reduce both timeline and quality risks in a development program, he says. Having this prior experience will allow a CDMO to adequately support device development-related activities, including early feasibility studies and design verification activities.

The CDMO can also collaborate with device developers to tailor drug product filling parameters to meet device-critical quality attributes such as break-loose and glide force, plunger

insertion depth precision, and bubble size control. Finally, a turnkey CDMO will also be responsible for drug container/device integration, and must understand the critical quality requirements associated with the final device assembly steps.

OWEN MUMFORD: Recognizing the Importance of Safety Design

With the continued growth in both biologics and biosimilars for subcutaneous delivery, these formulations present challenges related to volume of injection, viscosity, and injection time. Hence, there is an increased need to deliver higher volumes of biologics (greater than 1mL) via subcutaneous injection. This has led to the emergence of safety devices for 2.25mL PFS, enabling higher volume administration and the benefit of potentially less frequent injections for the patient. These safety devices are designed to prevent needlestick injury as well as enabling patients to administer medication at home.

"At Owen Mumford, we recognized the problems that result from the presence of springs in the design of safety devices for PFS," says George I'ons, Head of Product Strategy & Insights at Owen Mumford. "Issues such as pre-activation in transit or before use, which ultimately impact the patient, were the motivation in developing the product and removing the spring from the design." As a result, Owen Mumford's UniSafe is a spring-free device, which has a less intimidating appearance and allows the user to clearly see and check the drug before use.

"We also realized that creating an integrated plunger that could not easily be removed from the rear of the syringe, especially during RNS removal, was key to preventing spillage and waste, and providing tamper evidence," he says.

Solving these two issues, as well as creating a platform product that could address delivery of higher volume drugs or biologics lead Owen Mumford to create UniSafe in both 1mL and 2.25mL presentations. In addition, a desire to address sustainability concerns has resulted in development work to produce a reusable autoinjector with UniSafe 1mL at its core, which is expected to be on the market in 2022.

UniSafe® 2.25 is the latest addition to the established UniSafe® platform from Owen Mumford.

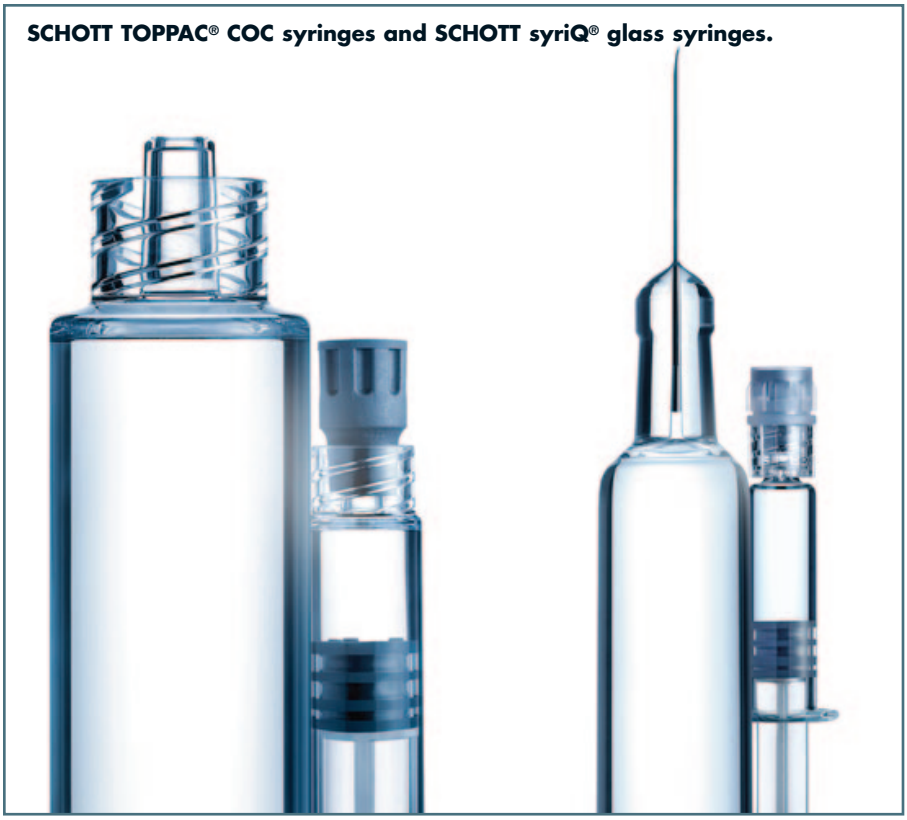
SCHOTT: Getting Prepared For COVID-Ready PFS

The COVID-19 pandemic saw the rise of mRNA-based therapeutics. But a major challenge is the cold temperature storage and supply chain. mRNA degrades easily and in order to allow for injection in the human tissue, the mRNA is encapsulated in lipid nanoparticles. The shelf life of this complex system is prolonged by storing the drug at extreme low temperatures, as low as -80°C. These low temperatures provide new hurdles for the primary packaging.

Currently, most COVID-19 vaccines are launched in vials to allow for fast time-to-market. However, prefillable syringes could become a good alternative. Fewer drug preparation steps means a lower risk for medical errors. Additionally, single-dose PFS have the potential to minimize drug waste, compared to multi-dose vial packaging, which has a limited shelf-life once opened, says Tom van Ginneken, Senior Global Product Manager for SCHOTT. This becomes especially relevant with the potential outlook of a yearly re-vaccination – not at a vaccination center – but at the doctor's office.

"While we see many benefits in the use of PFS for mRNA-based therapeutics, a PFS is a much more complex system compared to vials with more drug-contacting components: rubber plunger, rubber closure, lubrication layer, and in some syringes, the

SCHOTT TOPPAC® COC syringes and SCHOTT syriQ® glass syringes.



needle and glue," he says. "And, little is known about how a PFS reacts to -80°C storage and transport. The rubber components used for the closure and plunger have different thermal expansion rates than the syringe material, and at the extremely low temperatures the elastic properties of the rubber components could be impacted, which may ultimately risk container closure integrity. Another challenge is the stability of the lubrication inside the syringe. This layer is typically a variation of silicone oil. After freezing and thawing, this silicone layer could create small particles that may impact the stability of the mRNA-encapsulated lipid nanoparticles."

SCHOTT is investing $1 billion for capacity expansion across all pharmaceutical packaging product groups, and is working with mRNA biotech companies and universities to better understand the interaction between primary packaging and mRNA-based drugs. SCHOTT has characterized syringe functionality, sterility, and container closure integrity at extreme low temperatures of -80°C. As a next step, Mr. Ginneken says SCHOTT will investigate the lipid nanoparticle stability with glass syringes as well as cyclic olefin copolymer (COC) syringes.

"In combination with the analytical expertise from SCHOTT Pharma Services, SCHOTT is ideally positioned to help biotech companies choose the right pharmaceutical container or transition from vials into PFS," he says.

TERUMO PHARMACEUTICAL SOLUTIONS: End-User Safety Is Top of Mind

Increasing patient comfort during parenteral therapies is paramount at Terumo Pharmaceutical Solutions, which offers a comprehensive portfolio of needles, infusion sets, and primary packaging solutions.

"The patient is our end user," says Katsuyuki Takeuchi, Associate Product Manager, Terumo Pharmaceutical Solutions. "Everything we do should always take into account the patient and we must always ask ourselves if we are improving things for end users. As we supply our products to pharma companies, we also rely on our customers to incorporate the patient's perspective right from our first interactions on a project."

Where possible, Terumo engages closely with patient groups to fully understand real-world challenges with drug and injection devices. Just recently, the Terumo team conducted a research project among the hemophilia community to see how its devices (in this case, safety-winged infusion sets) are used. "Our aim was to gather insights into the daily activities of patients and see where we could improve on the process of administering medication," explains Mr. Takeuchi. "These important insights will fuel our future innovations and ensure the voice of the patient is embedded in the projects we pursue. Overall, the pharma industry is open to engage in multi-party discussions to support complex project discussions, and ultimately get products onto the market in an efficient way with reduced timelines."

Again, with the patient top of mind, Terumo pays close attention to stringent regulatory scrutiny aimed at ensuring patient safety. Additionally, Mr. Takeuchi says there are changes in the regulatory landscape, like the change in the EU from the Medical Device Directive (MDD) to the Medical

Terumo Pharmaceutical Solutions PLAJEX™ ready-to-fill polymer syringe.

Device Regulation (MDR).

The new regulation is four times as long and the word safety appears 290 times, compared to 40 in the MDD. "These regulatory changes pose specific challenges to the industry and increased demand for customization," he says. "With the uptake of small-scale/virtual biotech companies, which require additional support and services compared to global pharma players, we are in a position to offer a comprehensive documentation package to our customers to support them in their filing activities with the authorities. Regulatory filing, especially for combination products, requires close cooperation between all parties involved to make pathways to market shorter."

There is also the issue of self-injection safety. Terumo's PLAJEX™ primary packaging solutions offer the functionality and compatibility to deliver biologics and parenteral drug products.

The product is assembled with a 2-step autoinjector. Patients simply remove the cap and press the device onto the skin to complete the injection. The single-dose use medication is also suitable for elderly patients on continual treatment.

WEST: Patient Needs & Complex Drugs Drive Development of Delivery Devices

Because a large share of the global population is living with at least one chronic health condition – such as autoimmune disorders, cancer or diabetes – today's patients have an increased need and a growing preference for easy-to-use, reliable, self-administered medications for frequent injections. Pharmaceutical companies are responding to these needs by rapidly developing new drug and delivery solutions. In fact, in the context of the COVID-19 pandemic where many patients are hesitant about in-person clinical visits, these innovative solutions can help patients manage their conditions safely at home.

Treatment options for chronic diseases are often managed through novel biologics. Biologics account for the majority of drugs in development pipelines and can be challenging to administer because of their complex structure and sensitive nature. Selecting the right materials for packaging and drug delivery is critical in improving stability and mitigating performance risks. Therefore, greater scrutiny is paid to the interaction between the drug and its container closure system. Drug stability over the shelf life, particulate burden, the prevention of breakage, and ease of delivery are important factors to consider. In addition, regulatory agencies and pharmaceutical companies have increased quality expectations to enhance patient safety.

"Delivery systems based on cyclic olefin polymers (COPs) are becoming increasingly popular because these materials can meet the challenges of providing the quality, safety, and reliability needed for complex therapeutic applications," says Dr. Nicolas Brandes, Director, Product Management, Polymer Prefilled Syringes and Vial Containment, West. "Benefits of COP-based syringes include break resistance, superior functional performance, highly reduced extractables, and low particulate burden."

He adds that high-quality COPs, such as the Daikyo Crystal Zenith® syringe, are designed to overcome complex drug challenges, provide solutions for unique user requirements, and add value to complex and sensitive biologics. This includes the absence of silicone oil in Crystal Zenith syringes, which decreases interaction with the drug product and significantly reduces particulate load. "The Crystal Zenith Insert Needle Syringe supplied with a Daikyo Flurotec® piston is designed to maintain the pu-

"The Daikyo Crystal Zenith® Insert Needle Syringe is designed to maintain purity, integrity, and efficacy of premium biopharmaceutical therapies (West).

rity, integrity, and efficacy of premium biopharmaceutical therapies," says Dr. Brandes. "The Crystal Zenith Insert Needle Syringe, coupled with an autoinjector device, provides greater patient convenience and ease of use through self-administration."

Finding fill-finish options for the broad variety of drug product packaging and containment options can be a challenge for drug developers. West provides fill-finish support services and assists with small-scale sample preparation for product testing, fill-finish implementation support, third-party clinical and commercial filling, analytical testing, and program management. "Having a single partner with these capabilities in fill-finish requirements for innovative containment systems, such as the Daikyo Crystal Zenith polymer syringe technology is critical," he says. "Using a pharmaceutical services partner with experience in support services can reduce development and supply risk, reduce total cost of ownership, and accelerate a path to market. West's Simplify the Journey™ process does exactly that: it partners with drug developers from concept and development, through to analytical testing, assembly, and regulatory filing, to streamline the commercialization of drug delivery systems – no matter the complexity."

Crystal Zenith and Daikyo Flurotec are registered trademarks of Daikyo Seiko, Ltd. ◆

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BIOSCIENCE

Lexaria Bioscience Corp.: Stretching Its Legs

Lexaria Bioscience Corp. is a publicly traded biotechnology company focused on the development and commercialization of its patented DehydraTECH™ drug delivery platform technology. Lexaria's technology is mainly designed for improving the systemic absorption of orally administered lipophilic compounds, although it has also been shown to be effective in enhancing systemic delivery through the topical administration route. Lexaria began developing its DehydraTECH technology in 2014 and has since demonstrated its applicability and utility across a broad range of lipophilic drugs and beneficial compounds. Lexaria has grown significantly over this time with a state-of-the art, Health Canada-licensed formulation laboratory in Kelowna, British Columbia, as well as contract formulation and/or production laboratories operating in Salt Lake City, UT, and Atlanta, GA. DehydraTECH technology is currently protected by 18 issued patents spanning the US, Europe, and Australia, with roughly 60 additional patent applications pending worldwide. *Drug Development & Delivery* recently spoke with John Docherty, President of Lexaria, to learn more about how the company's recent uplist to the NASDAQ has resulted in its largest capital injection to date, which will allow it to focus on preclinical and clinical testing programs for DehydraTECH formulations across three main areas of interest: cannabidiol for treatment of hypertension; antiviral drugs for treatment of COVID-19 and other infectious diseases; and reduced risk oral nicotine products for CPG and/or pharmaceutical purposes.

Q: Can you describe the pain point you see in pharma and how DehydraTECH addresses that challenge?

A: By enhancing the oral deliverability of lipophilic drugs and beneficial molecules, Lexaria's DehydraTECH can address important medical and market needs for the pharma industry across three key areas. First, the technology enhances effectiveness whereby DehydraTECH formulations have been shown to significantly increase speed and quantity of absorption into both the bloodstream and even brain tissues thereafter for certain CNS-active agents. Second, it can improve tolerability whereby DehydraTECH's ability to enhance effectiveness can, in turn, often allow reduced dosing for any given effect profile, thereby mitigating unwanted side effects. Finally, there is a potential to expand ease of access and breadth of distribution in cases where lipophilic drugs are currently only available in injectable formats that could possibly be transitioned to effective oral formats using DehydraTECH. All three of these potential pharma benefits are, for instance, top of mind priorities for Lexaria in its present pursuit of safer and more effective oral antiviral therapies for certain COVID-19 therapies that are only available today in injectable form.

Q: Can you expand on how DehydraTECH works to enhance absorption and oral delivery, and how delivery is enhanced across the GI barrier and within brain tissue?

A: Lexaria's patented DehydraTECH formulation and processing methodology involves combining a lipophilic active ingredient with certain types of fatty acids – mainly long chain fatty acids (LCFA) – at a molecular level by way of a dehydration technique that it has developed. DehydraTECH formulations are rendered as highly stable powders that can then be integrated into a wide variety of solid oral dosage forms or even food products, or additional processing steps can be employed to integrate these powders into oral consumable liquids and topically administered form factors as well. Once administered, DehydraTECH formulations enable enhanced systemic delivery of their active ingredient "payloads" because of the emollient properties of their fatty acid compositions for enhanced permeation of epithelial/mucosal tissues and, most notably, upon intestinal exposure because they work in concert with biliary functionality that naturally promotes rapid lymphatic uptake of LCFA-containing materials. DehydraTECH formulations have also been shown to lead to enhanced blood-brain-barrier permeability, which Lexaria believes is due to fatty acid transport proteins that are found throughout the vasculature of the brain and naturally facilitate uptake of LCFA-containing materials.

Q: How is Lexaria taking DehyraTECH from the CPG space to the pharma space.

A: Lexaria's early work beginning in 2014 and 2015 was focused almost entirely on applications of DehydraTECH for the cannabinoid CPG sector, whereby it demonstrated proof-of-principle *in vitro*, *in vivo* animal, and human data with molecules such as cannabidiol, and out-licensed its technology to multiple players in the space. Following this, Lexaria began to explore applicability of its technology to more highly regulated CPG product applications, such as the nicotine product sector, for which it issued a non-exclusive worldwide license to Altria in 2019 and entered into an R&D collaboration with British American Tobacco during 2020. Most recently, in late 2020 and early 2021, Lexaria has begun to focus on the pharma space as it is pursuing expanded programs testing DehydraTECH-CBD formulations for hypertension therapy and DehydraTECH-antiviral formulations for COVID-19 and other infectious disease applications. Lexaria believes the greatest commercial opportunities and potential for its DehydraTECH technology lie in the pharma space for these and a multitude of other therapeutic applications. This is not dissimilar to the way that GW Pharmaceuticals took what was effectively a generic version of CBD and accomplished the admirable achievement of getting it approved for use to treat certain seizure disorders, eventually leading to a multi-billion corporate transaction.

Q: Digging a bit deeper, can you share some of the study data that shows how DehydraTECH improves drug delivery of antiviral therapies, such as Remdesivir?

A: Lexaria recently announced findings from an animal study that demonstrated that its DehydraTECH technology significantly enhanced systemic drug delivery of representative drugs from two classes of antivirals actively under investigation today for COVID-19. These included a protease inhibitor (darunavir; 54% increase in AUC∞; p=0.036) and a reverse transcriptase inhibitor (efavirenz; 42% increase in AUC∞; p=0.028). Based on these findings, the company is actively pursuing a further

round of animal testing to determine if DehydraTECH can similarly enhance the delivery of Remdesivir as another type of reverse transcriptase inhibitor actively in use for COVID-19 treatment today; specifically, a nucleotide reverse transcriptase inhibitor (NtRTI). In parallel, Lexaria is going to perform work to assess the relative antiviral activity of DehydraTECH antiviral formulations in an established cell culture model of SARS-CoV-2-infected cells, with a view to expanded efficacy testing thereafter in SARS-CoV-2-infected animals.

Q: How can DeydraTECH benefit other injectables, and what does this mean for COVID-19 treatment?

A: If Lexaria's upcoming and planned *in vitro* and *in vivo* animal PK/PD testing with DehydraTECH-powered antiviral formulations, including Remdesivir, prove successful, this could lead to broad applicability potential for a host of different lipophilic antiviral drugs for safer and more effective oral formulations for a variety of prospective indications, including COVID-19 treatment. Of course, any positive findings from Lexaria's upcoming and planned work described here would need to be subjected to further extensive characterization and testing in humans to determine if animal findings translate to man safely and effectively before commercial prospects could be determined.

Q: How large of a market is the antiviral therapy sector?

A: Pending the successful outcome of Lexaria's upcoming and planned proof-of-principle antiviral formulation and testing studies, it envisions seeking out opportunities to engage with developers of leading antiviral therapeutics for COVID-19 and other infectious disease conditions. Companies like Gilead would be a logical target for this outreach, given its work on the class-leading Remdesivir therapeutic that has received emergency use authorization by regulators around the world, but is currently limited to injectable administration. Remdesivir alone has been predicted to reach $4.2 billion in sales for treatment of COVID-19 and other infectious diseases by 2023.[1]

Q: Beyond the aforementioned applications, how will Lexaria advance the development of DehydraTECH formulations?

A: While our immediate focus through early-to-mid 2021 is going to be in advancing development of our DehydraTECH-powered formulations for hypertension, antiviral, and reduced-risk nicotine applications, Lexaria is stretching its legs to see where it can take DehydraTECH. We are very interested in exploring a range of other bioactive substances of interest to the company, spanning NSAIDs, PDE5 inhibitors, estrogen, vitamin D3, and pharmacokinetic evaluations with certain minor cannabinoids. We believe that DehydraTECH formulations across each of these molecule classes and others could represent additional significant opportunities for the company, pending successful proof-of-principle testing and subject to our out-licensing business model, if strategic partner interest is as high as we expect.

Q: What is Lexaria's out-licensing business model?

A: Lexaria has a successful track record of conducting proof-of-principle development programs using its DehydraTECH technology and effecting licensing arrangements with consumer-facing companies. Lexaria is focused on commercializing its DehydraTECH technology through out-licensing arrangements with third-party pharmaceutical and CPG industry partners. Lexaria already has established relationships with companies in the nicotine CPG sector, including a license arrangement in place with Altria, and an R&D collaboration actively underway with BAT (British American Tobacco). Lexaria similarly intends to seek out relationships with market leaders in its other product pipeline focus areas as its ongoing proof-of-principle development programs advance. Lexaria also routinely is contacted by third parties with interest in exploring DehydraTECH applicability across other molecule classes, whereby it often performs formulation development work on a fee-for-service basis and can offer commercial-scale DehydraTECH formulation capabilities to CPG companies via its contract partner facility in Salt Lake City.

Q: How does Lexaria work with companies that are looking to improve the delivery of their drug molecules?

A: In cases where companies approach us interested to determine if DehydraTECH can improve delivery of their specific drug molecules, we typically enter into mutual due diligence discussions under NDA, followed by bench-scale, non-GMP formulation development and QC testing work in order to render demonstration materials for the companies to receive and evaluate. This work is generally conducted under the framework of a letter of intent agreement between the parties, with a view to prospective DehydraTECH licensing and full technology transfer if the party is satisfied with the outcome of their evaluation testing work upon the demonstration materials furnished. In some cases, we do also have the ability to offer commercial-scale DehydraTECH formulation capabilities to CPG companies via our contract partner facility in Utah, in the event companies do not have these capabilities in house and/or do not wish to become licensees; instead preferring to simply purchase DehydraTECH batch materials on a purchase order fee-for-service basis from us, as needed.

Q: What does uplisting to NASDAQ mean for Lexaria?

A: Lexaria was delighted to complete its NASDAQ uplisting and a concurrent, oversubscribed $11 million institutional financing in January of this year. This signified a major validation of the company and its development programs, and has provided its largest capital injection to date in order to aggressively pursue its technology and formulation development plans. Graduating to a senior US National Exchange gives the company a solid footing to access the widest possible investor and capital base going forward as it continues to grow and evolve in the years to come. ◆

Reference

1. Remdesivir Global Market Report 2020-30: COVID 19 Growth and Change, Reportlinker, July 2020, https://www.reportlinker.com/p05933761/Remdesivir-Global-Market-Report-30-COVID-19-Growth-and-Change.html?utm_source=PRN#backAction=1.

INJECTABLES MANUFACTURING

Manufacturing Injectable Devices: Why Modern Means Modular

By: Raffaele Pace, MMe, MBA

INTRODUCTION

If steadily emerging trends in the parenteral pharmaceuticals landscape have taught us anything, it is this: one injectable device most certainly does not fit all. Without innovation, patients would find themselves… well, stuck. Today's drug delivery devices must be more mobile, less intrusive, and simpler than ever before – all while remaining cost competitive.

Several factors are driving this. For starters, more and more treatments are moving from the hospital to the home, which saves costs for healthcare providers while increasing patient comfort. Already a trend leading into 2020, this push toward at-home healthcare has only been exacerbated by the COVID-19 pandemic, when hospitals themselves can be dangerous environments for patient treatment.

FIGURE 1

With modular manufacturing, the goal is to produce equipment solutions that can repeat what typically requires repeating while still remaining flexible for more customized capabilities.

Meanwhile, over the past several years, the pharma industry has seen a steadily-building trend – one in which the demand for injectables has been consistently growing. Much of this is attributed to the increase in chronic diseases that often require consistent self-administration to ensure proper treatment. The most prominent of these is diabetes, which has long been a problem in the developed world and is now becoming more widespread in developing, large-population nations like India and China. Other instances in which self-administration of injectables come into play are the growing niche of targeted small batch and even personalized medicines, including oncological formulations and certain biologics.

SELF-INJECTION MEANS CUSTOMIZATION

With injectables moving more and more from hospital to home, the need for user-friendly injectable devices becomes clear. As such, it is not surprising that pen devices and auto-injectors have become exceedingly popular, as they deliver drugs efficiently while mitigating the typical risks associated with self-administration via syringes. These risks include incorrect dosing, device misuse, heightened discomfort, and from an adherence standpoint, greater potential for regimen discontinuation.

For pharma companies to continue staying cutting edge and cost competitive, these shifting end-user trends will necessitate a "managing backward" approach to manufacturing optimization. Starting with the unalterable result – injectables will increasingly be both customized and self-administered, whether we want them to be or not – this should, for efficiency's sake, affect the process stretching all the way back to inception: the design, engineering, and production of the assembly line equipment tasked with manufacturing devices such as auto-injectors or pen injectors. Increasingly in this growing genre, custom-designed equipment, automation, flexible and scalable manufacturing lines, and alternative manufacturing approaches will be critical to achieving timely, successful product launches.

From an infrastructure investment standpoint, the equation is simple: More customized medicines delivered via a broader array of injection devices means a premium is placed on equipment flexibility and modularity.

Although many injector types have similar components, their designs vary significantly in terms of size, material, and shape. This is a major production challenge, especially for contract manufacturing organizations that cater to pharmaceutical customers around the world. The variety of shapes, sizes, components, configurations, and other variables are too exponential to calculate.

Like the pen injectors and auto-injectors themselves, the equipment-centric solution to this conundrum is multifaceted. To keep up with the needs of modern combination products, assembly machinery needs to check a number of boxes.

The first is fast format changeover, which allows manufacturers to expediently handle different formats (pens with variations) and save on costly downtime. The other two are flexibility and scalability. Injection devices assembly is Exhibit A as to why a viable, future-ready pharma production process must embrace and exhibit the ability to adapt to changes in product volumes, demand, and sub-categorical issues like target audience differentiation. Flexible equipment enables manufacturers to meet production variations, or handle even different devices on the same line, ideally eliminating the need for an entirely separate line configuration. Further, it allows reduced CAPEX investments and achieve shorter time to market. To accommodate planned or sudden scale-up processes, the equipment should be scalable and "future-proof," designed in a manner that allows additional modules to meet increased volumes.

Another factor is automation, which at first glance may seem to contradict the need for smaller batches and customizable delivery devices. Injectables manufacturing increasingly involves a push-pull in which, while lower commercial production volumes are commonly required, manufacturers also must be capable of efficiently switching gears to more far-reaching, wider-scale production efforts. Furthermore, even when batches will remain on the smaller side indefinitely, automating certain processes – for example, tool-free changeover – can reduce human intervention and further decrease production downtime.

In both cases, the mission-critical ability to proficiently pivot is where automation and robotics come into play. At this stage, the common denominators in which automation becomes valuable are reliability, precision, repeatability, and process optimization. The goal is to incorporate these elements at the very inception of the development process, allowing for flexibility to test multiple solutions at a low scale of production and, as the process evolves, have an "automation foundation" in place to expeditiously increase output. The more and the earlier a manufacturer can automate, the more efficient the ramp-up process is likely to progress.

In a landscape where each unique project increasingly requires an equally

FIGURE 2

When one size doesn't fit all, the best solutions are rearrangeable solutions – ones that align with modern, mandated assembly line versatility.

unique solution complete with its own development and investment schedule – again, one largely devoid of "off-the-shelf" options – a push toward platform-level solutions is underway. This initiative has allowed efficiency-minded companies to pre-configure many elements of an automation line, as part of "preplanning" the process for progressing projects from early R&D through clinical trials and wider production, however large the in-market batches.

BUILDING PRODUCTION SUCCESS FROM THE FOUNDATION UP

When one size doesn't fit all, the best solutions are rearrangeable solutions – ones that align with modern, mandated assembly line versatility. Simply put: if one production line doesn't fit all… then you must have the building blocks to configure a broad array of them, depending on project-specific needs. Combined with transport platforms and process modules that help streamline production planning and workflow from initial prototyping to full-scale production, this modular approach will help more pharma manufacturers meet an already-dizzying array of specialized injectables needs now and into the future.

From an equipment aspect, modularity is the primary prerequisite for flexibility and scalability. Increasingly, pharma manufacturers will favor machinery vendors capable of building equipment solutions that are simultaneously tailor-made and agnostic; in other words, lines whose current setup is ideal for the project at hand but reconfigurable to address inevitably shifting needs. This points squarely toward lines that can be efficiently adjusted to address tomorrow's often ill-defined needs and easily reconfigured for similar projects – all while offering required levels of customization.

To enhance speed-to-market, modular line assemblies – such as those developed by Stevanato Group – can comprise a range of customizable platforms and modules aligned with commonalities across a wide array of projects. The goal is to produce equipment solutions that can repeat what typically requires repeating while still remaining flexible for more customized capabilities.

VIEW FROM THE FACTORY FLOOR

Here's what this looks like on an everyday basis. At a project's inception, a manufacturer would typically commence the prototyping phase with a benchtop, then increase production at an early stage by multiplying benchtops and operators – generally one person per benchtop. As an alternative approach, it is advisable to develop a semi-automatic pilot line, which reduces risks related to human intervention and, because it makes the overall process more automated, offers inherent scale-up advantages. In this scenario, an initial investment mitigates risks for future steps as the same technologies are being utilized for both the pilot lines and eventual large-scale, fully automatic line.

Among other benefits, this approach minimizes risks through early debugging and the ability to add scale without the need to re-invent or completely reconfigure the assembly processes.

As the production stages progress, each platform has an increasing range of available modules that can perform assembly, inspection, labeling, and packaging processes. This modular approach

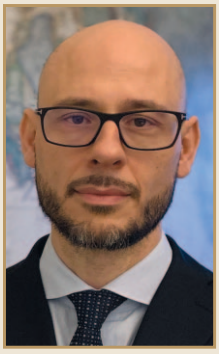
enables forward-thinking equipment providers to rapidly engineer tailor-made solutions that deliver consistent performance, high-quality standards, and proven reliability when scaling-up to higher volumes… all built on a consistent, proven foundation. This provides opportunities for greater flexibility to adjust to new device configurations, different device formats, or production requirements.

The benefits found by realizing optimized, modular automation are many. The validation timeframe can be reduced – hastening speed to market – and technology-validated processes become significantly simpler, mitigating any associated risks. Modularly is also, by its very nature, synergy-centric; it encourages engineering and production teams to work in harmony by planning, in parallel, for near-term and longer-range scaling needs.

This building block approach brings another benefit: an inherent ability to grow a line in direct alignment with the production phase. Once each process is validated, manufacturers can proceed from the current automation level to the next one, easing a rapid scale-up. In addition, by utilizing assembly operations with the same module from benchtop platform through large-scale industrial line, these validation processes are minimized both individually and collectively.

Revisiting the speed-to-market aspect, this multi-stage mindset helps expedite the overall process by performing stability or clinical studies in tandem with planning for future scale up. These can be accomplished with robotic systems designed for higher volumes, reliability, and flexibility. Here, involving equipment partners with modularity experience from the early stages offers a distinct advantage, since they've seen for themselves how initial development work is crucial for establishing early proof of principle and validating the assembly process. ◆

BIOGRAPHY



Raffaele Pace is Engineering Vice President of Operations at Stevanato Group, a leading producer of glass primary packaging and provider of integrated capabilities for drug delivery systems. A licensed engineer, Mr. Pace earned his MBA from the Università di Bologna and his Master's Degree in Mechanical Engineering from Università della Calabria. He has more than 15 years of experience developing complex equipment and line configurations.

Specialty CDMO

Adare Pharma Solutions is a global technology driven CDMO providing turnkey product development through commercial manufacturing expertise focused on oral dosage forms for the Pharmaceutical, Animal Health and OTC markets. Adare's specialized technology platforms provide taste-masking, ODTs, and customized drug-release solutions. With a proven history in drug delivery, Adare has developed and manufactured more than 40 products sold by customers in more than 100 countries globally. For more information, visit Adare Pharmaceuticals at **www.Adarepharmasolutions.com.**

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Ajinomoto Bio-Pharma Services is a fully integrated contract development and manufacturing organization with sites in Belgium, United States, Japan, and India providing comprehensive development, cGMP manufacturing, and aseptic fill finish services for small and large molecule APIs and intermediates. Ajinomoto Bio-Pharma Services offers a broad range of innovative platforms and capabilities for pre-clinical and pilot programs to commercial quantities, including: Corynex® protein expression technology, oligonucleotide synthesis, antibody drug conjugations (ADC), high potency APIs (HPAPI), biocatalysis, continuous flow manufacturing and more. Ajinomoto Bio-Pharma Services is dedicated to providing a high level of quality and service to meet our client's needs. For more information, contact Ajinomoto Bio-Pharma Services at **www.AjiBio-Pharma.com.**

Parenteral Manufacturing

ApiJect Systems, Corp is a medical technology company that revolutionizes how the world manufactures and delivers injectable medicines and vaccines. The ApiJect technology platform brings together simple, interconnectable components to create scalable drug delivery devices for US and global markets. At the center of these devices is the aseptic and cost-effective Blow-Fill-Seal (BFS) fill-finish process. And, by using a modular manufacturing approach, these devices can be produced in clinical or commercial scale by ApiJect or the drug manufacturer. Our first device, the single-dose ApiJect Prefilled Injector, allows a healthcare professional to twist a pen needle-style hub onto a BFS container — creating a simple, scalable prefilled syringe. ApiJect is working with several vaccine pharmaceutical companies to conduct the testing and regulatory reviews of COVID19 vaccines in the ApiJect Prefilled Injector. For more information, visit Apiject Systems at **www.apiject.com.**

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With the Covid-19 pandemic infecting millions around the world, time-to-market is of the essence for drug developers. **Aptar Pharma's** PremiumCoat® platform for vial stoppers and syringe plungers combines a pure bromobutyl rubber formulation with a market-proven ETFE film-coating, reducing extractables and leachables. Our state-of-the-art manufacturing processes and automated visual inspection guarantee high quality with low particulate specifications. Our extensive data packages for PremiumCoat stoppers support your evaluation of our solutions to help mitigate risks. These packages include vial/stopper compatibility, multi-piercing testing, container closure integrity, extractables files for regulatory submission, and simulation studies (probable leachables). PremiumCoat stoppers are adapted for multi-piercing applications and have been validated for Covid-19 vaccines, including mRNA. Our platform approach helps you anticipate the switch to Pre-Filled Syringes for long-term vaccination strategies. For more information, visit Aptar Pharma at **www.aptar.com/pharmaceutical/**.

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Parenteral Delivery Devices

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Parenteral Delivery Solutions

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Vetter is a leading contract development and manufacturing organization (CDMO) that specializes in the aseptic filling and packaging of syringes, cartridges, and vials. The company has extensive experience with biologics and other complex compounds. Collaborating with pharma/biotech clients worldwide, Vetter supports products from preclinical development through global market supply. Through its US and European facilities, Vetter Development Service provides state-of-the-art support for early stage products, with transfer at Phase 3 to Vetter Commercial Manufacturing for large-scale production. For more information, visit Vetter at **www.vetter-pharma.com.**

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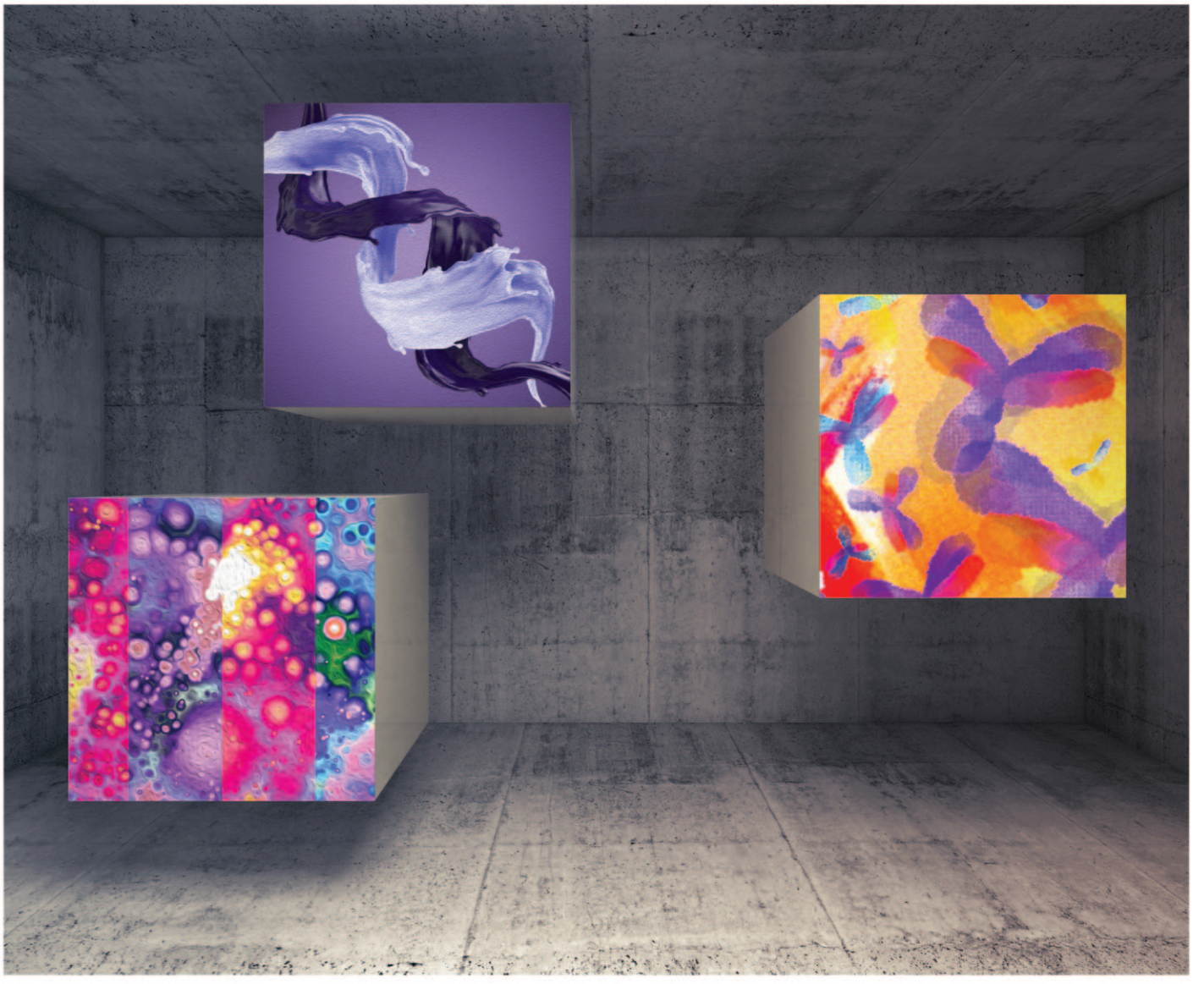

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